



KMJ

KUWAIT MEDICAL JOURNAL

The Official Journal of The Kuwait Medical Association

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Article

Burrows B, Lebowitz MD. The β agonists dilemma (editorial). *N Engl J Med* 1992; 326:560-561.

Book

Roberts NK. The cardiac conducting system and His bundle electrogram. New York, Appleton-Century-Crofts, 1981; 49-56.

Book chapter

Philips SJ, Whisnam JP. Hypertension and stroke, In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p 465-478.

Weblinks

U.S. positions on selected issues at the third negotiating session of the Framework Convention on Tobacco Control. Washington, D.C.: Committee on Government Reform, 2002. (Accessed June 4, 2003, at http://www.house.gov/reform/min/inves.tobacco/index_accord.htm.)

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Editorial

When is Time to Change?

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Kuwait Medical Journal 2008, 40 (1): 1-2

After almost thirty years of existence the Faculty of Medicine at Kuwait University has undertaken a reform of their undergraduate medical curriculum and now has a modern, case-based, problem based learning (PBL) medical program being rolled out. Without the usual external drivers of change, it usually takes far more inner resolve to achieve this successfully. In the UK, it was the General Medical Council (GMC), responsible for educational and professional standards, which forced through curricular reform according to their blueprint described in *"Tomorrow's Doctors"*^[1]. In the US, similar initiatives have taken place and almost three-quarters of medical schools have adopted some form of PBL strategy.

However, this round of curricular reform has been far more challenging than those that came before. The changes have come at a time when educational institutions increasingly are being held accountable for their activities, usually through the process of accreditation. But the Faculty of Medicine, Kuwait University, is achieving change without either a powerful external driver or a process of accreditation that could be used to shape and support change. With discipline based educational ownership being passed to a central Faculty Administration there are all the ingredients for conflict. Some say this is just a painful generational change from the traditional to the modernists, who espouse openness and debate and reject isolationism and intransigence. This openness is often forgotten by the reformers whose haste leaves little time to inform and articulate their vision for reform. All reformers shall be both informed and prepared to inform, otherwise dissent is inevitable. Students too, have often been forgotten, becoming the foot soldiers on the battlefield. This is wrong, and their contributions are also an essential ingredient for successful reform.

What's so wrong with the traditional medical curriculum that it needs fixing? First and foremost,

it is overloaded with non-essential content that has accumulated like the barnacles on an unscrubbed ship, gleaming on the topsides yet almost unseaworthy below the surface, unseen by those who choose not to look. We know how little is retained from a lecture delivery, and yet the traditional curricula has thousands of them. Medical knowledge and practice almost completely changes every ten to fifteen years, and soon will have an even shorter shelf life, and yet we have not prepared our new doctors to cope with this change. Deficiencies have been seen, debated and discussed endlessly, often progressing no further. Curricular reform is a time to address all these issues.

First, Howard Barrows started a new medical program in the late sixties with his vision for developing the skills of clinical reasoning through a process called PBL^[2]. Then, came Ron Harden, a true modernist, who showed the starting point of reform with his SPICES model^[3] in the early eighties. What was common to both these pioneers was the centrality of the student learning process. Considerable attention was being paid to two facets of the process, what the product should actually be and how adult learners would get there. All this change has created other problems that still wait to be fully addressed. For example, secondary school education was unprepared to meet these new challenges and often just continued to turn out students for traditional teacher centred tertiary education. Kuwait may be temporarily stuck in this groove. But the voices of the consumers are powerful ones and must be listened to.

Kuwait University's Faculty of Medicine is now introducing modern educational philosophies and strategies and should be supported: their new curriculum is fully integrated, employs case-based PBL, has a skills-program and early clinical exposure, has introduced modern and validated assessment techniques and uses a stringent quality control

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process, right from the lecture hall to the examining process. But there is more, tomorrow's doctors shall be able technologists and computer literate. As part of the Faculty vision, the curriculum will soon be fully supported by an Electronic Learning Project: this is an electronic curriculum that allows students to plan their learning according to their study style and pace. The web-based delivery platform incorporates a framework of learning objectives and theme outcomes comprehensively linked to all the study resources provided both by the teaching staff as well as selected sites on the internet. Theoretically, a medical student from Kuwait can continue their studies with full support and access to all the usual learning materials while visiting family in the US.

So why are there any detractors? There are probably two major concerns: the first is that graduates from these modern programs are not as well equipped academically as their predecessors and the second is that many universities have not kept pace with the structural changes that a modern curriculum has on the activities of many Faculty staff. Many universities just continue the same outdated mantra about teaching hours for tenure, without first seeking to find out whether this form of appraisal is still valid. The answer to the first concern is that there is no evidence that exam results are prejudiced and many examples abound^[4-7]. Interestingly, those who are the detractors were trained in traditional curricula and judge graduate results from new curricula the same way they were themselves judged, the whole thing becoming an outdated self-fulfilling prophecy. The very reason for the reform of medical training was to produce

a different sort of doctor, not clones of an earlier time. Universities with any pretention to modernity should be informed about changing teaching methods and the developments taking place in their institutions. While at the same time it has been found that the single greatest mistake made by most champions of change is that insufficient time and attention has been paid to communicating their vision and plans to the stakeholders.

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Review Article

Amplifiers of Systemic Inflammation – The Role Advanced Glycation and Lipoxidation End Products in Foods

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ABSTRACT

Chronic diseases are repeatedly associated to accumulation in the body of glycated and lipoxidated proteins and peptides. PubMed reports in excess of 5000 papers plus about 14,000 articles about the related HbA_{1c}, RAGE, a member of the immunoglobulin super-family of cell surface molecules and receptor for advanced glycation end products, functions as a master switch, induces sustained activation of NF- κ B, suppresses a series of endogenous auto-regulatory functions and converts long-lasting pro-inflammatory signals into sustained cellular dysfunction and disease. RAGE is activated by high levels of dys-functioning proteins in body fluids and

tissues and is strongly associated with chronic diseases from allergy and Alzheimer to rheumatoid arthritis and urogenital disorders. Heat-treatment, irradiation and ionization of foods increase the content in foods of advanced glycated end-products (AGE) and advances lipoxidated end-products (ALE). Some processed foods, much like tobacco smoking are major contributors to accumulation of glycated and lipoxidated molecules in the tissues. Change of life style: avoidance of foods rich in deranged proteins and peptides and increased consumption of antioxidants, especially polyphenols counteracts such a development.

KEY WORDS: antioxidants, acute diseases, chronic diseases, foods, glycation, inflammation, lipoxidation, Maillard products

INTRODUCTION**Epidemic of Chronic Diseases**

Chronic diseases (ChD) constitute today the leading cause of morbidity and mortality. World Health Organization (WHO) estimates that 46 % of global disease burden and 59 % of global mortality is due to ChD; 35 million individuals die each year from chronic diseases, and it increases steadily^[1]. The fastest increase in ChD is in recent years was seen in the Third World – there are today more cases of type 2 diabetes in India (44 million) and China (22 million) than in the US (17 million) and this increase continues in these countries as in the rest of the world. The picture is similar for most ChDs. It appears as if we in the Western world export the ChDs together with our lifestyle with our enormous surplus of cheap agricultural products: dairy products, especially milk powder and butter, and grains, especially wheat. Little consideration seems to be given to the fact that a large proportion of individuals in these parts of the world are gluten or lactose intolerant and are deficient in the local production of health-promoting fresh fruits and vegetables, rich in nutrients, antioxidants and

health-promoting lactic acid bacteria (LAB).

The increase seems to have begun at the time of the industrial revolution, *e.g.* mainly in the early and middle 19th century. Circumstantial evidence supports an association of ChDs to change in lifestyle with less physical activity, increased mental and physical, stress and transition from natural unprocessed foods to processed, calorie-condensed and chemically modified foods. The food consumption during the last 150-200 years is characterized by significant reduction in intake of plant fibers, plant antioxidants and n-3 polyunsaturated fatty acids (PUFAs), a more than doubled intake of saturated and trans fatty acids (from app 20% to > 40% of daily energy intake) and a > 100-fold increase in high glycemic index (GI) foods: sugary and starchy products - the annual consumption of refined sugars has increased from about one lb per person per year in 1850 to about 100 lbs/person/year in the year 2000.

IMPAIRED INNATE IMMUNE FUNCTIONS

Common to most of the food ingredients mentioned above is that they affect the function

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of the innate immune system, the inflammatory response and the individual's resistance to disease. While plant fibers, antioxidants and to some extent PUFAs enforce resistance to disease, saturated and trans- fatty acids, sugar and starch, peptides such as gluten, and many chemicals and pharmaceuticals, including antibiotics, suppress resistance to disease. Consequently, most ChD patients suffer increased acute (APR) and chronic (CPR) phase response, increased inflammation/super-inflammation and metabolic syndrome (MS) – (see further Bengmark)^[2]. Important observations are that saturated fat, as well as trans fatty acids, induce significant alterations in the immune response^[3], inhibit the macrophage functions^[4], stimulate Th2 response relative to the Th1 response and increase the risk of getting chronic diseases such as diabetes, certain cancers and rheumatoid arthritis^[4]. It has not been given the attention it deserves that exposure to some chemicals including supply of pharmaceutical drugs such as antibiotics will suppress macrophage functions demonstrated for antibiotics by studies of chemiluminescence response, chemotactic motility, bactericidal and cytostatic ability and of lymphocyte proliferation^[5,6].

ADVANCED GLYCATION AND LIPOXIDATION

It is almost 100 years since Malliard described the non-enzymatic pathway for glycation of proteins and suggested that such chemically modified proteins could play a role in the pathogenesis of ChDs, particularly diabetes^[7]. However, it is only in the last two decades, particularly the last five years, that this concept has received a wider attention. Contributory to the increased interest in recent years is the observation of glycated hemoglobin, HbA_{1c}^[8,9] and its role in diabetes and in various aging-associated diseases, and particularly the identification of several receptors in the body, of which RAGEs are the most well-known and studied^[10,11]. Presently in excess of 5000 papers about the biology of advanced glycation products are to be found on PubMed in addition to the > 13,500 about HbA_{1c}.

RAGE – A MASTER SWITCH

Metabolic syndrome with all its clinical manifestations is strongly associated with development of ChDs. Recent studies suggest that a chronic low-grade inflammation foregoes and plays an important role in the development of and maintenance of metabolic syndrome^[12] and in pathogenesis of ChDs. Common to different ChDs are, in addition to a subinflammatory state, a significantly elevated oxidant stress (OS) and OS-induced gene expression^[12-15]. Much support that receptor for advanced glycation end-products

(RAGE) and various other receptors for advanced glycation (AGEs) and also lipoxidation (ALEs) end products play a central role in the genesis of these changes. RAGE, a member of the immunoglobulin superfamily of cell surface molecules, is known to convert long-lasting cellular activation into sustained cellular dysfunction/disease^[16]. RAGE seems to function as a master switch, converting proinflammatory signals into long-lasting, often permanent cellular dysfunction^[17]. This is done as RAGE induces a sustained activation of proinflammatory transcription factor NF-κB and suppresses a series of endogenous autoregulatory functions^[18]. Reducing the inflammatory environment through reduction in accumulation in the tissues of AGE and ALE ligands has also been shown to reduce or eliminate sustained exaggerated inflammation and cellular dysfunction and to improve outcome of disease – see further^[16,19].

LIFE-LONG ACCUMULATION OF AGEs AND ALEs

As pointed out by Vlassara^[19], industrial processes aimed to make food safer, flavorful and colorful, such as heating, irradiation and ionization, do all, in combination with gross over-nutrition, significantly contribute to production of, exposure to and accumulation in the body of AGEs / ALEs. Vlassara and her group has also in human studies demonstrated significant correlation between ingested AGEs, circulation AGEs and induction of several markers of inflammation^[20,21]. Furthermore, they demonstrated in animal studies that dietary restriction of AGEs has “protective” effects against impaired immune function in various ChDs and complications to ChDs, particularly diabetes-induced vasculopathy^[22], nephropathy^[23] and impaired wound healing^[24]. And most interestingly, these animals remained close to ‘free from pathology’ state despite the presence of the underlying disease^[19]. Furthermore, dietary AGE restriction seemed in animals to be as effective to extend life span as caloric restriction^[25]. These observations are partially confirmed in humans with diseases such as diabetes, vascular disease and kidney disease, who responded with a considerable reduction in markers of inflammation and vascular dysfunction when supplied a low-AGE diet^[20,26].

AGE's constitute a complex, heterogenous and increasing group of compounds formed mainly by nonenzymatic reactions of reducing sugars with amino acids, nucleic acids, peptides and proteins, which produce early compounds called Amadori products, which later through a so called Maillard reaction undergo complex changes such as cyclization, dehydration, oxidation, condensation, cross-linking and polymerization to form irreversible

chemical products referred to as Maillard products or AGEs/ALEs. In particular, reactive carbonyls such as glyoxal and methylglyoxal have been found to rapidly modify reactive side chains of proteins. The ϵ -amino group of lysine and the guanidino group of arginine are identified as the most preferential targets for the highly reactive dicarbonyls, which makes lysine and arginine-rich tissues and foods special targets for these processes. High intracellular and extracellular concentrations of reactive carbohydrates such as glucose, but even more the highly reactive fructose, are important triggers for increased glycation and formation of glyoxal, methylglyoxal and 3-deoxyglucosan, which glycates protein and sooner or later form intracellular and extracellular accumulation of AGEs/ALEs. Significantly elevated visceral AGE formation, serum AGE levels, caspase-3 activation and cytoplasmic DNA fragmentation in organs such as heart, liver and kidneys are regularly observed in animals with dyslipidemia due to high-fat diet (32 - 42% fat)^[27], all in line with 50 year old observations that high-fat diet-induced increased rate of diseases such as myocardial infarction, renal infarcts and thrombus formation^[28].

Glyoxal and methylglyoxal formation constitutes an intermediate stage in the Maillard reaction, while pentoside, an often studied glyco-oxidation product and fluorescent cross-link, is formed in the late stage of the reaction, where it becomes stable and irreversible. Many AGEs in tissues have been identified, but most studies are performed in only a few of them: in addition to HbA_{1c} mainly AGEs such as pentoside and/or N^ε-carboxymethyl lysine (CML) and N^ε-(carboxyethyl)lysine (CEL). However, new, previously unknown AGEs are identified at a rate of 2-3 per year^[29]. Furthermore, there is increasing evidence that accumulation of chemically modified lipids in the tissues are as important contributors as carbohydrates to development of diseases^[30]. It is especially the lipids in milk products and meat that, when these foods are heated up, contribute substrate for production and accumulation of ALEs in the tissues. A typical AGE such as CML, seems to be formed from both carbohydrate and lipid sources^[31]. Examples of specific AGEs are pentoside, crosslines, vesperlysines and 3DG-imidazolones while malondialdehyde (MDA) acrolein adducts of lysine, histidine and cysteine are specific examples of ALEs – see further^[31].

A great variety of different AGEs/ALEs are observed in the tissues and in the circulation of patients with ChDs, and common to most, if not all ChDs is that the levels are significantly increased compared to healthy individuals. Irrespective of source, both AGEs and ALEs, when accumulated in tissues do significantly induce increased

Table 2. Cytokines and cellular events associated with AGE or RAGE activation

VCAM-1 ↑	Endothelial cells
ICAM-1 ↑	Endothelial cells
E-selectin ↑	Endothelial cells
PDGF ↑	Pancreatic cancer cells
eNOS ↓	Endothelial cells
Tissue factor ↑	Endothelial cells
TGF-β ↑	Mesangial cells, proximal tubular cells, vascular smooth muscle cells, macrophages
TNF-α ↑	Endothelial cells, mesangial cells, mononuclear macrophages
IGF-1 ↑	Mesangial cells
MCP-1 ↑	Mesangial cells, endothelial cells
CTGF ↑	Fibroblasts, mesangial cells
IL-6 ↑	Endothelial cells
PAI-1 ↑	Endothelial cells
RAGE ↑	Mesangial cells, endothelial cells, podocytes
VEGF ↑	Podocytes, endothelial cells, mesangial cells
ANG II dependent cell activation ↑	Vascular smooth muscle cells
Type IV collagen expression ↑	Mesangial cells
Fibronectin ↑	Mesangial cells
Cell cycle progression ↓	Fibroblasts, mesangial cells

eNOS, endothelial nitric oxide synthase; TGF-β, transforming growth factor-β; MCP-1, monocyte chemoattractant protein-1; CTGF, connective tissue growth factor; PAI-1, plasminogen activator inhibitor-1.

Fig. 1: Documented cellular events and changes in cytokines associated with AGE and RAGE activation (after Bohlender *et al*)^[128]

inflammation and infection^[32,33], reduce antioxidant defense^[34], weaken immune system^[35], impair DNA repair mechanisms^[36] and accumulation of toxins in the tissues^[32]. Most importantly, they accelerate the rate of development of various ChDs. And the differences are great - glycated proteins are suggested to produce almost 50 times more free radicals than nonglycated proteins^[37]. The plasma concentrations of free CML and CEL are for example increased about 8-fold and 22-fold, respectively, in hemodialysis patients^[38].

LONG-LIVED MOLECULES / TISSUES ARE SPECIAL TARGETS

Cumulative AGEs/ALEs modification of tissues occurs predominately on long-lived molecules such as collagen, neural myelin and lens crystallins resulting in insoluble, indigestible and dysfunctional compounds that accumulate with time. The crosslinking of glycated collagen leads to decreased elasticity of collagen-rich tissues, which explains the age- and ChD-dependent increase in stiffness of joints and skeletal muscles and lenses, but also of cardiovascular system with increased blood pressure^[39]. AGEs/ALEs exert strong effects on endothelial cells and pericytes: stimulate growth, interact with cell-surface receptor RAGE and activate the NF-κB pathway, induce vascular endothelium growth factor (VEGF), inhibit prostacycline production and stimulate plasminogen activator inhibitor-1 (PAI-1) synthesis by endothelial and other cells. Fig. 1 summarizes documented cellular events and changes associated with AGE and RAGE activation.

Of special interest is that these processes seem all to be sensitive not only to oxidants/antioxidants but also to a large extent to hormones, especially growth and sex hormones. 17 β -estradiol has been shown to significantly upregulate RAGE mRNA and protein level in human microvascular endothelial cells^[40]. This could explain the common observation that diabetic vasculopathy and retinopathy are often exacerbated in pregnancy. 17 β -estradiol in concentrations observed during pregnancy (~ 10 nM) stimulates significant up-regulation of VEGF-dependent angiogenesis^[41]. It is also observed that effects induced on endothelial cells by 7 β -estradiol and RAGE mRNA are totally abolished by supply of antiestrogens such as 4-OH tamoxifen^[41]. This knowledge might explain why commercial bovine milk, known to be rich not only in AGEs/ALEs but also in estrogens including 17 β -estradiol, is often associated with different ChDs such as allergy^[42], coronary heart disease^[43,44], diabetes^[45-47], Parkinson's disease^[48] and various cancers such as breast^[49,50], prostatic^[51,52], testicular^[51] and to some extent ovarian^[53,54] malignancies. Secondary hyperparathyroidism, due to poor supply of vitamin D, especially at higher altitudes (where incidence of ChDs and rate of complications to ChDs are significantly higher during winter), seem also to play a significant role^[55,56]. Parathyroid hormone is known to induce IL-6 and levels of serum IL-6 have been shown to significantly increase in hyperthyroid patients (16-fold) and in overweight patients – see further^[55].

THE ROLE OF AGE/ALE TISSUE DEPOSITION IN COMMON CHDs

Deposition in sensitive tissues of abnormal proteins, often as amyloid is a common feature of various ChDs. These deposits are AGEs/ALEs and are known to produce fluorescence. The degree of ALE/AGE deposition can be relatively easily and reliably measured, especially in organs such as the skin, blood and lenses, through estimation of the degree of fluorescence^[57]. The content of AGEs/ALEs seems to always increase with aging, also in healthy individuals. However, this increase is considerably more pronounced in individuals who will or have acquired various ChDs. It is increasingly recognized that activation of RAGE plays a key role in pathogenesis of various ChDs. Increased deposition of AGEs/ALEs in tissues is also strongly associated to metabolic syndrome and also to downregulated leptin expression in adipocytes^[58-60].

Here follows a short summary of some common ChDs and their association to AGE/ALE-induced changes:

Allergy and autoimmune diseases: Thermal processing, curing and roasting of foods introduce

major changes in allergenicity of foods, and is likely to introduce neoantigens and increase allelgenicity. However, further studied are needed, especially as sometimes reduced allergenicity has also been reported^[61-62]. Heated foods such as milk, peanuts and soy are, however, reported to significantly influence levels of AGEs and the IgE-binding capacity^[63,64]. Significantly elevated levels of urinary AGEs such as pentosine have been observed in children in connection with exacerbation of atopic dermatitis^[65].

Alzheimer disease (AD) and other neurodegenerative diseases: Similarities between Alzheimer and type 2 diabetes (T2DM) exist to the extent that Alzheimer has been called “the diabetes of the brain”. The incidence of AD is also reported to be 2 to 5-fold increased in T2DM – see further^[66]. A common feature of both diseases is accumulation of amyloid deposits, a process, which progresses during the whole course of disease. AGEs/ALEs in AD are identified immunohistochemically both in senile plaques, in tau proteins, amyloid β proteins and in neurofibrillary tangles^[67,68]. A threefold increase in content of AGE is also reported in AD brains compared to age-matched controls^[69] supporting a role of AGEs in the pathogenesis of AD. The olfactory bulbs, early targets of AD, also show significant increase in AGE and markers of oxidative damage^[69]. Furthermore, increases in RAGE protein and in percentage of RAGE-expressing microglia are reported to parallel the severity of disease^[70]. Among the changes observed are, in addition to amyloidosis, perturbation of neuronal properties and functions, amplification of glial inflammatory response, increased oxidative stress, increased vascular dysfunction, increased A β in the blood brain barrier and induction of autoantibodies - see further^[70]. Early indications suggest, although this is less studied, that AGEs/ALEs are also involved in the pathogenesis of other neurodegenerative diseases such as Parkinson's disease (PD)^[71,72], amyotrophic lateral sclerosis (ALS)^[73-75], Huntington's disease^[76], stroke^[77], familial amyloidotic polyneuropathy^[78] and, most interestingly, in Creutzfeldt-Jakob disease^[79]. Early accumulation of AGEs is also observed in Down's syndrome and early antiglycation treatment suggested to reduce cognitive impairments^[80]. It was recently suggested that bovine spongiform encephalopathy, a disease with its significant similarities to Alzheimer, is also associated with increased glycation and lipoxidation^[81]. AGEs, amyloid fibrils and prions all seem to have the same target: RAGE and they all do activate the NF- κ B pathway^[81]. Frey suggests, but no studies are yet performed, that glycation will have the capacity

to activate prion proteins. What is clear is that the feeds of dairy cows has in recent decades changed significantly, as has Western foods, from mainly forage-based feeds to that containing more of starch-rich and fast-absorbed carbohydrates: corn, maize grains, barley, molasses and dextrose. Such feeds will most likely induce resistance to insulin (in cows if the cows were allowed to live long enough) and development of diabetes. Insulin resistance has also been observed in intensively milk- and lactose-fed calves^[82].

Arteriosclerosis and cardiovascular diseases:

Oxidative stress, lipid peroxidation and protein glycation have repeatedly been associated with extensive arteriosclerosis. A recent study reports significant increases in both chemical AGEs (carboxymethyllysine) and fluorescent AGEs (spectrofluorimetry) in 42 patients with atherosclerosis when compared to 21 healthy controls ($p < 0.001$)^[83]. Increased levels of malondialdehyde, lipid peroxides and pentosidine were found recently in a study of 225 hemodialysis patients shown to be significantly and positively correlated to coronary artery calcification score (CACS)^[84]. Increased development of atherosclerosis and deposition of AGE/ALES in the arterial walls, in parallel to a significant increase in lipid oxidation, was observed when rabbits were fed a diet containing 1% cholesterol or 1% cholesterol + 10% fructose in drinking water, and especially so in the fructose-complemented group^[85]. High density lipoproteins (HDL) will, when subject to structural modifications by lipoxidation, glycation, homocysteinylolation or enzymatic degradation, lose their anti-inflammatory and cytoprotective properties^[86]. This has been suggested to be of importance in the pathogenesis of not only arteriosclerosis, but also in neurodegenerative diseases, diabetes and other autoimmune diseases^[87]. Dendritic cells (DCs) are known to play an important role in the pathogenesis of arteriosclerosis. A recent experimental study demonstrates that supplementation of AGE-modified serum albumin increased levels of cytokine secretions, increased maturation of DCs and augmented capacity to stimulate T-cell proliferation^[88].

Cancers: The influence of AGEs/ALEs on the pathogenesis of malignant tumors and their ability to grow is not extensively studied. However, it is reported that the sRAGE receptor, highly expressed in healthy lung tissues and especially at the site of alveolar epithelium, is significantly downregulated in lung carcinomas^[89] and the RAGE expression is reported to be elevated in human pancreatic cells with high metastatic ability and low in tumour cells

with low metastatic ability^[90]. High RAGE expression is also reported in colonic^[91] and prostatic^[92] cancers. Little information is, however, available about other types of cancers, including breast cancer, but it has recently been suggested that inhibition of AGE-RAGE interaction might have a potential as a molecular target for both cancer prevention and therapy^[90-92].

Cataract and other eye disorders: AGE/ALEs accumulate with age in all ocular tissues including lacrimal glands and trigger pathogenic events, especially in diabetics, in all parts of the eye^[93,94].

Diabetes (DM): Over-consumption of fat and carbohydrates and not only of glucose but also other carbohydrates such as lactose and fructose, will significantly contribute to the accumulation of AGEs/ALEs in the tissues of diabetics. The consumption of high-fructose corn syrup in the US is today exceeding that of sucrose, and suggested to be the major contributor, not only to obesity and hepatic steatosis, but also to type 2 diabetes and to severe complications of both type 1 and 2 diabetes^[95]. Almost half of the publications about AGEs/ALEs or >2000 deal with their role in DM. Several excellent reviews are recently published^[96-98].

Endocrine disorders: Many, if not most of the signs and symptoms of aging, as well as age-associated diseases, are identical to manifestations seen in hormone deficiencies and in premature aging, a condition strongly associated with multiple hormone deficiencies. Most consequences of aging such as excessive free radical formation, imbalanced apoptosis system, tissue accumulation of waste products, failure of repair systems, deficient immune system, poor gene polymorphisms, and premature telomere shortening are also associated, if not caused by, with hormone deficiencies^[99]. Increased glycation and cross-linking of proteins are significant signs of aging, products known to especially accumulate in parenchymal organs, as shown in diabetes and chronic renal disease. Upregulation of putative pathological pathways; accumulation of AGEs, activation of the renin-angiotensin system, oxidative stress and increased expression of growth factors and cytokines are frequently observed in the settings of ChDs, but little information is available about the content of AGEs/ALEs in endocrine organs such as the pituitary gland, thyroids, parathyroids, adrenals, ovaries and testes in health and disease. However, increased AGE serum levels and activation of RAGE is reported in women with polycystic ovary syndrome^[100]. Activation of the renin-angiotensin system, known to have a pivotal role in ChDs such as diabetes and chronic renal

disease, potentiates the pathogenic mechanisms: increase advanced glycation, glycototoxicity and lipotoxicity and contribute to enhanced oxidative stress and inflammation and to increased levels of free fatty acids^[101-103].

Gastrointestinal disorders: It is likely that GI disorders such as liver cirrhosis and liver steatosis as well as inflammatory bowel disorders are associated with elevated AGEs/ALEs. A recent study reports a 14-16-fold increase of glyoxal-derived adducts in portal and hepatic venous plasma of cirrhotic patients compared to healthy controls^[104]. Plasma AGE levels were also measured in 51 patients with liver cirrhosis, five patients after liver transplantation and 19 healthy controls^[105]. Patients with liver cirrhosis demonstrated significantly increased AGE levels, almost to the same extent as seen in patients with end-stage renal disease. A dramatic improvement was observed in patients after liver transplantation, although the AGE levels did not return to the levels seen in healthy controls and the preoperative decrease in renal function also persisted. One hundred and ten patients with chronic liver disease (CLD) were recently studied and compared to 124 healthy controls. Serum levels of AGE (CML) were significantly affected by the stage of liver cirrhosis and closely associated with liver function capacity, and AGE (CML) level (reported to positively correlate with levels of hyaluronic acid (HA) ($r = 0.639$, $p < 0.0001$)^[106]. A recent animal study suggests that blockage of RAGE is highly protective against hepatocellular death and necrosis on ischemia and reperfusion (I/R) and increases significantly the rate of survival^[107]. Similar observations are also made in acetaminophen-induced hepatotoxicity in mice^[108]. In addition to increased survival, decreased hepatic necrosis and significant increase in glutathione and pro-regenerative cytokines TNF- α and IL-6 was observed.

Pulmonary disorder: Lack of homeostasis in oxidant/antioxidant balance is obvious in a variety of airway diseases, including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis and idiopathic pulmonary fibrosis. Interaction of AGEs/ALEs and RAGE plays, if not a dominating, at least a large role in the pathogenesis of these pulmonary diseases, and depletion of antioxidants, particularly GSH, in lung epithelial lining is thought to play a key role in these disorders^[109-111].

Rheumatoid arthritis and other skeletomuscular disorders: A very strong expression of RAGE and among the highest levels of AGE in the body are found in tissues with slow turnover, such as tendons, bone,

cartilage, skin and amyloid plaques. These changes are associated with change in color from white to yellow-brown, increased fluorescence, increased expression of proinflammatory cytokines, matrix metalloproteinases (MMP), especially MMP-1 and -9. These manifestations are likely to be responsible for the observed increased tissue stiffness and brittleness in structures such as intervertebral discs, bones tendons, cartilages, synovial membranes, and skeletal muscles and will most likely constitute a major pathogenic factor in diseases such as osteoarthritis^[112,113], rupture of intervertebral discs^[114], Achilles tendons^[115], eventually also of menisci, and rheumatoid diseases^[116-118] such as rheumatoid arthritis and fibromyalgia. A significant increase in glycation of myosin occurs with age^[119] which most likely contributes to age-associated muscular disorders. Observations in subjects with osteoporosis of significantly elevated levels of pentosidine and CML in serum^[120] and significantly increased pentosidine in cortical bone^[121] are of considerable interest. It has also been observed that the remodeling of senescent bone is impaired by AGEs both through stimulation of bone-resorbing cytokines and enhancement of bone resorption by osteoclasts^[122]. The role of bovine milk in prevention of osteoporosis can well be found to be opposite to what has been believed and claimed for decades, should future studies verify that osteoporosis is more due to interactions of RAGE and AGEs/ALEs than to lack of minerals.

Skin and oral cavity: Skin has a high density of RAGE receptors. AGEs/ALEs are known to accumulate in dermal elastine and in collagens and to interact with dermal fibroblasts, inhibiting their proliferation capacity. A ten time reduction in proliferation rate is described as normal in humans between the second and seventh decade^[123]. This might well explain the reduced healing capacity of age-related wounds, and especially chronic wounds such as those on the diabetic foot. It has also been observed that accumulation of AGEs/ALEs in the skin reflects the AGE/ALE deposition in the rest of the body to such a degree that skin autofluorescence has been suggested as a measure of cumulative metabolic stress and advanced glycation end products in the body^[124]. Skin autofluorescence is suggested to be so exact that it is able to predict progression of retinopathy and nephropathy in diabetes^[124] as well as mortality in hemodialysis patients^[115]. RAGE and AGE/ALE-induced apoptosis and enhanced loss of fibroblasts and osteoblasts is also regarded as a major pathogenic factor in periodontal pathology, especially in chronic periodontitis^[126]. A 50% increase in RAGE mRNA is observed in gingiva of diabetic patients compared with controls ($p < 0.05$)^[126].

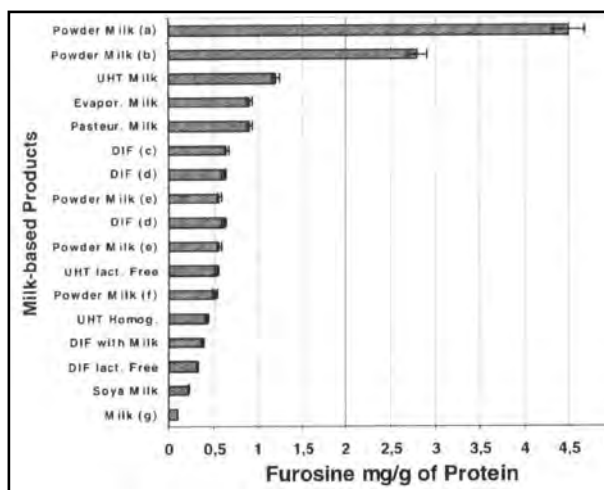


Fig. 2: Relative furosine content in various milk-based products. (a). Milk powder kept for two years at room temperature. (b). Milk powder kept for one year at room temperature. (c). DIF with whey plus casein. (d). DIF with hydrolyzed whey. (e). Milk powder kept for one year at 4 °C. (f). Fresh milk powder. (g). Raw (whole) bovine milk. DIF= dietetic infant formulas, UHT= ultra heat treatment (after Baptista JAB, Carvalho

Urogenital disorders: Nephropathy is common in the modern world and its incidence is fast increasing, much in parallel to the increase in diabetes. Diabetic nephropathy alone today affects 15-25% of patients with type 1 diabetes and as much as 30-40% of patients with type 2 diabetes. Furthermore, it is the single-most important cause of end-stage renal failure in the Western world^[127]. The kidney appears as both culprit and target of AGEs/ALEs, and it is well documented that RAGE is significantly activated and advanced AGEs/ALEs markedly elevated in renal failure patients. There are more than 500 papers on PubMed that deal with RAGE and AGEs/ALEs in renal diseases. A decrease in renal function and reduced clearance is observed much in parallel to increases in circulating AGEs. AGEs are also involved in the structural changes observed in progressing nephropathies such as glomerulosclerosis, interstitial fibrosis, and tubular atrophy^[128] – for detailed information, see recent excellent reviews^[128-133]. Patients with mild chronic uremic renal failure are reported to have plasma glycation free adduct concentrations increased up to five-fold and patients with end stage renal disease as much as 18-fold when on peritoneal dialysis and up to 40-fold on hemodialysis^[134]. Kidney transplantation is reported to improve but does not fully correct the increased AGE/ALE levels in previously dialysed patients^[135].

DIET-INDUCED INCREASE IN AGES/ALEs

By far the greatest of contributors of AGEs/ALEs seem to be dairy products, bread and meat, not only because they are all rich in these chemicals, but also as they constitute the bulk of modern food, especially in the Western world. Also plants

contribute to accumulation in the body of AGEs/ALEs, especially fruits, containing larger amounts of fructose, which is highly reactive with proteins and a large contributor to the development of AGEs.

Important AGE/ALE contributing foods are:

Diary products: Consumption of drinking milk is, although it has decreased during the last 50 years, still high in the Western world (USA 1950: 144 and 2000: 92 quarts per person and year). Instead it is, although at lower levels, increasing in other parts of the world, particularly in Asia (Japan 1950: 11 and 2000: 72 quarts/person/year). However, the consumption of cheese has quadrupled during the same period (USA 1950: 8 and 2000: 30 pounds/person/year; EU 2000: 38 pounds), to a large extent because of the increasing use in fast foods such as pizza, tacos, nachos, salads, fast-food sandwiches, and sauces for potatoes and vegetables. Also the global production of whole milk powder (WMP), which unfortunately contains much more of AGEs/ALEs than plain milk, has increased dramatically and continuous to do so (annual increase 2.7%) and is expected to reach 9.5 billion pounds in the year 2010.

It is unfortunate that it is AGEs/ALEs that to a large extent provide palatability to foods. This, in combination with the low price, might explain why milk powders increasingly are used as ingredient in food products such as bread, baby formulas, clinical nutrition formulas, chocolate, ice-cream, reconstituted milk and hundreds of other common foods. A milk product, which is reported to be especially rich in AGEs/ALEs, is custard. Ten to 20 %, sometimes up to 70 %, of the amino acid lysine is reported to be modified during common technological treatment (sterilization, pasteurization, irradiation etc.) of milk^[136]. Fructoselysine is the dominating modified molecule, but also CML, and pyrraline are produced during processing of milk^[136]. Content of sugars, level and time of elevated temperature and heat-exposure^[137], time and storage time contribute most to the production of AGEs/ALEs^[138]. Certain heavily processed cheeses such as Scandinavian “Mesost” and Norwegian “Brunost” contain especially large amounts of AGEs/ALEs (Brunost: 1691 mg CML/kg protein)^[139]. Microwaving of milk also increases dramatically the content of Maillard products^[140]. Fig. 2 illustrates the content of one Maillard product - furosine - in various dairy products, when fresh and stored for 1-2 years. It is important to observe that the already high amount in fresh milk powder increases four to nine times when the milk powder is stored for longer periods in room temperature (which is the standard today for baby formulas and often also for clinical nutrition solutions) in comparison to storage at 4 °C^[138].

Significant increase in numbers of both limited ($p < 0.001$) and extensive ($p < 0.001$) DNA-damaged cells has also been demonstrated on peripheral blood lymphocytes of infants fed cow's milk^[141].

Grains, cereals, bakery products: Consumption of bread is often associated with increased inflammation and ChDs, and is suggested to be associated with the content of proinflammatory molecules such as gluten in breads and grain products (especially those made of wheat, rye and barley)^[142]. Bread crusts and toasts and crisp breads such as rye crisps (Knäckebröd) are reported to be rich in AGEs/ALEs. Bread crusts are often used in animal experiments to increase the content in the body of AGEs/ALEs when the aim is to study the effects of these compounds on bodily functions. Fresh whole bread contains about 0.5 kU/g of AGEs/ALEs and toasted bread is reported to provide about 30 kU/serving^[143]. Pancakes (10 kU/g) and cereals such as Rice Krispies (Kellogg Co. Battle Creek MI – 600 kU/serving) and particularly toasted waffles and biscotti (1000 kU/serving) are other sources of large amounts of AGEs/ALEs^[143]. Pretzels (500 kU/serving) in contrast to popcorn (40 kU/serving) are also rich in AGEs/ALEs^[142].

Meat, poultry and fish: The content of AGEs/ALEs in beef, chicken and tuna fish is reported to be about similar (50 – 60 kU/g) although the content depends much on the method of preparation. The AGE/ALE content in for example, chicken breast is reported to increase as one goes from boiling to oven frying: boiling (1000 kU/serving) < roasting (4300 kU/serving) < broiling (5250 kU/serving) < deep frying (6700 kU/serving) < oven frying (9000 kU/serving)^[143]. Other compounds produced when beef, poultry and fish are heated above 100 °C are carcinogenic compounds called heterocyclic amines, and its amount produced increases with increasing temperature, and increasing presence of sugars and fats^[144].

Vegetables: Only few studies exist and most of them focus on effects of processes such as maturation, curing, and roasting and heat-treatment of plant products, mostly nuts and beans. Thermal processing alters significantly both biophysical and immunological properties of vegetable proteins such as peanut proteins: their structure, function, solubility, digestibility, immunoglobulin E (IgE) binding, and T-cell response^[145]. Curing at higher temperatures (> 77 °C) increases significantly both the levels of AGEs and the IgE binding capacity^[146].

Coffee, tea, alcohol and beer: The coffee bean, like the untreated tobacco leaf, when fresh and

unprocessed is extraordinary rich in powerful antioxidants, but when roasted at high temperature, it becomes a rich source of AGEs/ALEs. This is much in contrast to various teas, and particularly green tea and yerbamate tea, which to a large extent maintain their richness in strong antioxidants and ability to inhibit both protein nitration, second phase glycation reactions, and prevent the free-radical mediated conversion of the early so called Amadori products to irreversible AGEs^[147,148]. Consumption of an AGE-rich food such as coffee (200 ml/day) is also reported to increase serum levels of CRP by 30%, TNF α by 28% and IL6 by 50%^[149]. Alcohol is cytotoxic mainly due to its main metabolite acetaldehyde (AA), a main contributor of AGEs/ALEs. AGE fluorescence is observed to be significantly higher in alcohol abusers than in healthy subjects with a more modest alcohol consumption^[150]. Barley undergoes significant glycation during the malting process^[151], which is said to provide the foaming properties to beer^[152]. Beer is also a rich source of AGEs/ALEs. It is likely, although no studies are available, that dark beer contains more AGEs/ALEs than light beer. Similarly sugar-rich liquors might contain considerably more of AGEs/ALEs than pure and plain aquavit.

DIETARY MEASURES TO REDUCE AGEs/ALEs

Vegan diet seems to induce statistically significant lower systolic and diastolic blood pressure, lower serum total cholesterol, low-density lipoprotein cholesterol, triglycerides, fasting blood sugar, less weight problems and less incidence of ChDs, especially diabetes and complications of diabetes. However, there are also problems with vegetarian (lactovegetarian and vegan) lifestyle, which need to be corrected, among them risk of shortage in vitamin B12, higher serum levels of homocystein and poor taurine status^[153]. It is of special interest that AGEs/ALEs are reported to be higher in longtime healthy lacto-vegetarians than in vegans and healthy omnivorous^[154]. One explanation could be, as suggested by these authors, a higher intake of fructose, especially since this carbohydrate is significantly more reactive with proteins than sucrose. Another explanation could be a higher consumption of various milk products, especially cheese and milk powder, to compensate for the lack of meat and fish in the diet.

Several measures have been shown to significantly decrease serum and tissue concentrations of AGEs/ALEs, among them:

Caloric restriction (CL): Evidence from animal studies shows that restriction in intake of AGE/ALE-rich food is an effective means of extending median life span, and preventing ChDs, much in the

same way as is observed with caloric restriction^[15]. However, there are only a few studies available in primates and almost no studies in humans. Significant benefits of long-term (2-11 years) CL in comparison to Western diet were recently reported from a study in healthy humans: blood pressure $102 \pm 10 / 61 \pm 7$ Vs. $131 \pm 11 / 83 \pm 6$ mmHg, CRP 0.3 ± 0.3 Vs. 1.9 ± 2.8 mg/l, TNF- α 0.8 ± 0.5 Vs. 1.5 ± 1.0 pg/ml, TGF- β 29.4 ± 6.9 ng/ml Vs. 35.4 ± 7.1 ng/ml respectively^[155]. Patients with rheumatoid arthritis (RA) on a low energy diet for 54 days demonstrated a significant reduction in RA disease activity paralleled by a significant reduction of urinary pentosidine^[156]. However, studies in other groups of ChD patients are generally lacking.

Vitamins and antioxidants: Glutathione (gamma-glutamylcysteinyl glycine [GSH]) is thought to be an important factor in cellular function and a strong defense against oxidative stress. Dietary GSH suppresses oxidative stress, reduces glycation and prevents diabetic complications such as diabetic nephropathy and neuropathy^[157]. Rich supply of vitamins A, C, E, and particularly B6, B12 and folic acid (Fig. 3) is emphasized^[158]. Vitamin D should most likely be supplemented, especially at higher latitudes^[50]. Several thousands of plant-derived chemo-preventive agents, polyphenols and many other, most often unexplored, substances seem to have potential to reduce the speed of aging and prevent degenerative malfunction of organs, among them isothiocyanates in cruciferous vegetables, anthocyanins and hydroxycinnamic acids in cherries, epigallocatechin-3-gallate (EGCG) in green tea, chlorogenic acid and caffeic acid in coffee beans and also tobacco leaves, capsaicin in hot chili peppers, chalcones in apples, eugenol in cloves, gallic acid in rhubarb, hisperitin in citrus fruits, naringenin in citrus fruits, kaempferol in white cabbage, myricetin in berries, rutin and quercetin in apples and onions, resveratrol and other procyanidin dimers in red wine and virgin peanuts, various curcumenoids^[159] the main yellow pigments in turmeric curry foods, and daidzein and genistein from the soy bean. These compounds have all slightly different functions and seem to complement each other well. Several, most likely the majority, of these substances are able to inhibit the second phase of the glycation process, *e.g.* the conversion of the Amadori products to AGEs. A significant number of animal studies support the health benefits of these antioxidants and AGE/ALE scavengers^[160,161] but human studies are still largely lacking.

Taurine, carnitine, carnosine, histidine: Taurine, a small sulphonic acid, is found in high intracellular concentrations in most cellular animal tissues, and

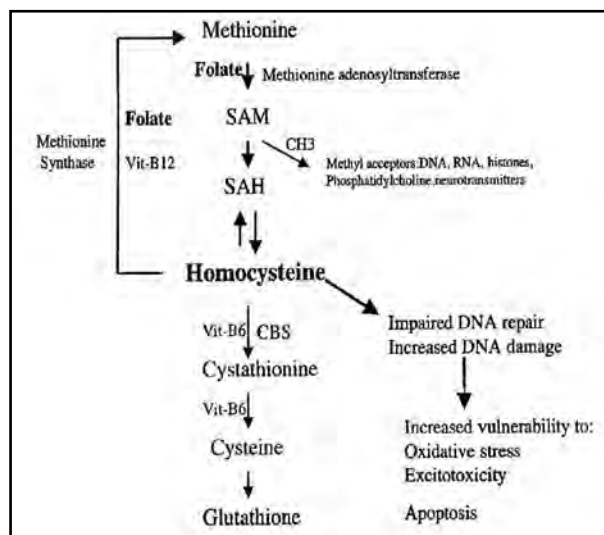
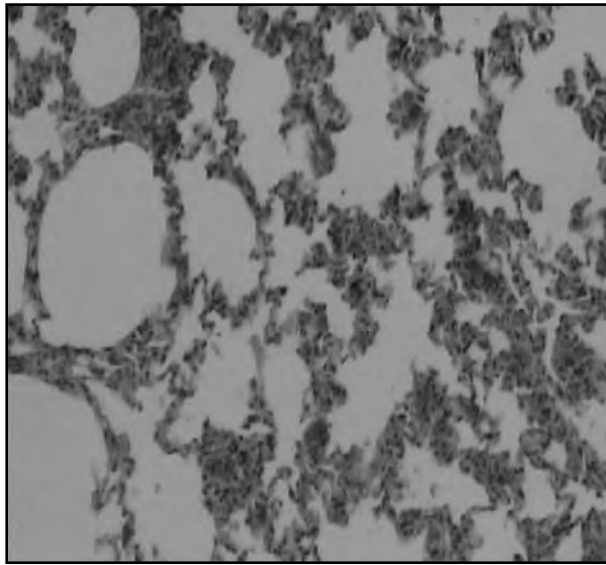


Fig. 3: Involvement of homocysteine folic acid and vitamin B6 and B12 influences metabolism and possible mechanisms whereby elevated homocysteine contributes to increased risks of chronic diseases (after Mattsson MP)^[158].

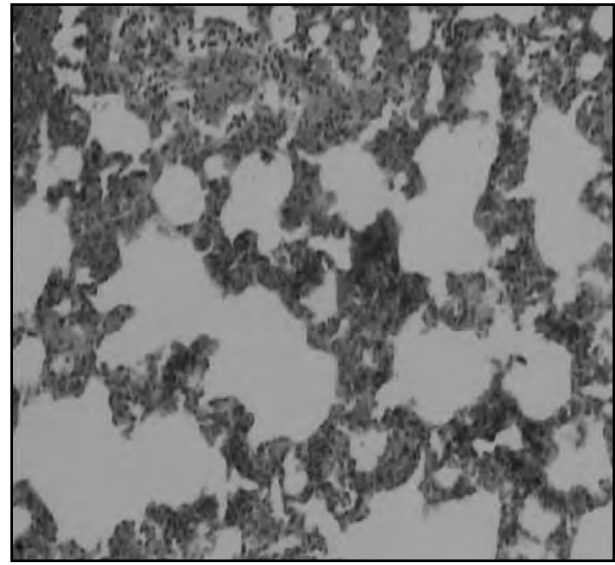
especially in blood cells, retina and nervous tissues. The highest concentration is found in neutrophils, where it is suggested to reduce inflammation^[162]. The richest sources of taurine is seafood, fish and poultry. Moderate amounts are also found in meat, while plants with the only known exception of some algae, and consequently vegan diets, are totally devoid of this amino acid^[163]. Taurine has also a well known strong hypoglycemic effect, known already since the 1930s^[164]. It reduces production of AGEs/ALEs, and prevents collagen abnormalities in high fructose-fed animals^[156,157]. *In vitro* as well as animal studies suggest that similar effects are obtained by supplementing amino acids or peptides such as histidine, carnitine and carnosine. However, again no human studies seem yet to have been performed.

Pre- and probiotics: All the various powerful antioxidants and AGE/ALE scavengers need, for the body to benefit from them, to be broken down and made available for absorption. This is almost entirely dependent on microbial enzymes, mainly provided by the flora in the lower gastrointestinal tract. However, the microbial flora is severely impaired in about 75% of omnivorous Americans and one third of vegetarian Americans^[167]. Lactic acid bacteria (LAB) are also in their own capacity strong oxidation scavengers and effective inhibitors of inflammation. LAB will most likely have the capacity to eliminate AGE/ALE protein and peptides from foods before resorption, as they have been shown to eliminate gluten^[168] and carcinogens^[169] from food. Support for such an assumption derives from an *in vitro* study, where fructoselysine, the main modified molecule in heated milk^[138] was

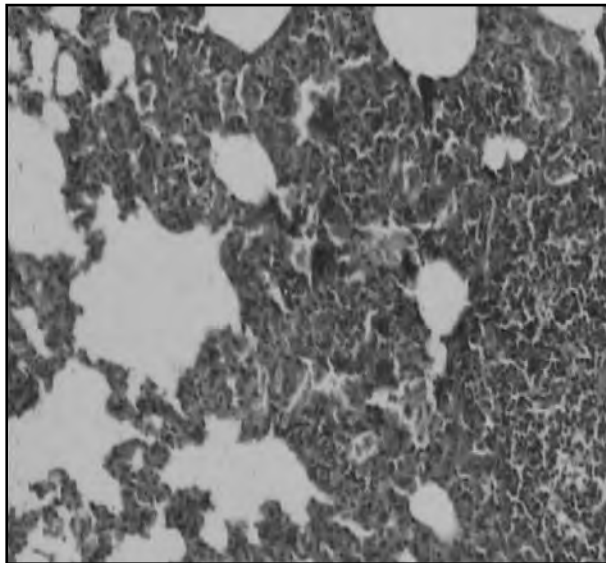
Fig. 4: A. B. C. Histological sections of rat lung 24 hours after cecal ligation and puncture. Mayers's heamatoxylin staining. Original magnification 100



A. After placebo treatment



B. After treatment with only bioactive fibers



C. After treatment with both bioactive fibers and live lactic acid bacteria (Synbiotic 2000). Photo by Dr Ozer Ilkgul, Izmir, Turkey

eliminated (deaminated) when incubated with live flora^[170]. Pretreatment before cecal ligation and puncture^[171] with oral administration of LAB in combination with prebiotic fibers (Synbiotic 2000 Forte, Medipharm, Kågeröd Sweden & Des Moines, Iowa USA) or subcutaneous injection^[172] with the same LAB prevented effectively increases in lung tissue of myeloperoxidase (MPO), malondialdehyde (MDA) and nitric oxide and most importantly, pulmonary neutrophil accumulation and lung tissue destruction (Fig. 4 A-C). In line with this is the observation that the same combination of LAB and fiber significantly downregulates expression of Toll-like receptors, reduces production of $\text{TNF-}\alpha$ ^[173] and significantly improves stage of disease (from Child C to B, or from B to A) in liver cirrhosis^[174].

FUTURE DIRECTIONS

Most studies in the past have focused on coronary heart disease, type 2 diabetes and chronic renal disease. However, increasing evidence suggests that an “unhealthy” life style is negatively associated with all ChDs. Common to most ChDs is a more or less permanent exaggerated inflammation, strongly associated with metabolic syndrome and also increased deposition in tissues of AGEs/ALEs. It is suggested that all ChD patients, including those with inherent genetic disorders such as Down's syndrome^[74,175], and cystic fibrosis^[176,177] but eventually also schizophrenia^[178,179] and mental depression^[180-182], diseases with obscure etiology but seemingly associated with increased oxidation and aberrant inflammation will benefit from measures to control AGEs/ALEs. Studies in the US demonstrate an 83% reduction in rate of coronary heart disease^[183], a 91% reduction in diabetes in women^[184] and a 71% reduction in colon cancer in men^[185] in patients adhering to what today is regarded as an “healthy lifestyle”. It is likely, but yet not proven, that control of intake and cellular production of AGEs/ALEs is an important ingredient in a healthy lifestyle, and might further improve outcome.

An exaggerated inflammation is also observed in patients, who suffer complications to acute diseases: infections, trauma and advanced surgical and medical treatments such as transplantations. Complications and sequelae to these events are significantly more common in elderly and particularly in those with ChDs. Much evidence supports that the lifestyle of the patients and degree of inflammation before trauma significantly affects outcome-see further^[186]. It is clearly documented that presence of metabolic syndrome does also in acute

morbidities negatively affect outcome. Recently accumulated knowledge about the link between metabolic syndrome and increased deposition of AGEs/ALEs in the body support the suggestion that future attempts to minimize accumulation in the body of such substances might significantly reduce both acute and chronic morbidities. However, the research in this field is in its early infancy, and most studies remain to be done.

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Original Article

Frequent Attenders at a Primary Health Care Center in Kuwait

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ABSTRACT

Objectives: To determine the frequency of general practice consultations and study personal and health factors associated with frequent attendance

Design: Retrospective descriptive and case control study.

Setting: Al-Surra Family Practice Health Center (SFPC), Kuwait.

Subjects: Three hundred seventy-two adults categorized as "frequent attenders" (FA) were included as cases. Three hundred sixty-eight adults categorized as "non-frequent attenders" (NFA) represented the controls.

Main Outcome Measures: Frequency of attendance to polyclinic and associated factors.

Results: A total number of 16,068 patients made 77, 970 visits to the SFPC during 2003. Out of them, 932 FA made 14,970 visits. The median number of visits per FA patient was 16, whereas it was only four for NFA. Only 45.5% of

frequent attenders presented with symptoms while 17.7% attended for repeated medical prescription, and 18.3% showed up for check-up. Logistic regression analysis revealed that Kuwaitis, governmental employees, females in older age groups with chronic illness were more liable to be FAs in general. Among Kuwaitis, governmental job and chronic disease were detected as significant risk factors for being FA. Chronic diseases were the only predictors of FA among non-Kuwaitis.

Conclusions: 5.8% of the total number of patients were responsible for 19.2% of the visits to SFPC. Chronic illness correlated strongly with a high rate of attendance. Also socio-demographic factors, especially nationality, gender, age and job type were indicators of frequent attendance in general practice.

KEY WORDS: consultation, contributing factors, frequent attendance, general practice

INTRODUCTION

There is no clear relationship between health need in the population and the workload in primary health care. 4.5% of patients accounts for one-fifth of the general practitioner's workload. Many people with clinically recognized symptoms do not seek medical advice. This phenomenon can be attributed to a combination of psychological and sociological factors. On the other end of the spectrum, frequent attenders (FAs) are a category of patients who attend health practice frequently, taking up time and whose management is often expensive and difficult^[1]. Most studies determined frequent attenders according to the number of visits per year^[2,3]. Since there has been no adequate methodological approach developed to study the frequent attendance phenomenon, the results of the studies dealing with this problem largely differ^[4].

A patient usually makes a visit to a family practitioner for their objective healthcare needs. However, patients often make unnecessary visits for various reasons, when their health condition

does not objectively require attendance by a health care professional^[5]. The main objective of this study is to determine whether frequent attendance is a natural occurrence that is representative of one end of a normal distribution of attendance, or is it unacceptable behaviour by a group of patients that are taking advantage of the easy access to healthcare in Kuwait^[6].

The phenomenon of frequent utilization of health care services is a multidimensional problem which can be analyzed from various points of view^[7]. Some studies focused on socio-demographic factors associated with frequent patient visits^[8,9]. Where morbidity is concerned, the most important causes of frequent visits were chronic diseases^[10,11]. However, depressive and neurotic patients as well as severely ill patients make visits to physician's office more frequently^[9,12]. It has been well established that female gender, increasing age, physical and psychiatric morbidity are all important factors in determining frequent attendance^[1, 2, 13-15].

As the phenomenon of frequent attendance

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has not been extensively investigated in the Gulf region, this study could serve as a model for a better understanding of the use of primary health care in this territory.

This study also aims to describe the frequency of attendance in general practice, and to study the effects of a range of factors that may be related to frequent attendance in adults.

SUBJECTS AND METHODS

General Practice in Kuwait

Seventy seven primary health care clinics are available in all residential areas in Kuwait. Working hours are extended daily from 7am -11pm to 24-hour operating clinics. The appointment system is applied on a very limited basis. The majority of workload at the clinic is conducted on an open access basis, depending on the availability of the physicians. Private medical practices at the primary care level are scarce in general and not available in Al-Surra area where this investigation was conducted.

Setting

This study was conducted in SFPC in Kuwait which served 27,271 inhabitants in 2003. Eight full-time working physicians were employed. Al-Surra is characterized as being predominantly inhabited by Kuwaiti families with few non-nationals. The majority of non-Kuwaiti inhabitants are middle-aged manual workers, who depend on Kuwaiti families and are primarily employed as housemaids, baby-sitters, drivers, gardeners or guardsmen.

Definition of Frequent Attenders

The number of visits made by the population of subjects during the study year was determined. Consultations with a medical service provider that was not registered as a doctor were discarded and each visit to the clinic was treated as a single entity regardless of the number of problems presented during the consultations. The third quartile of the figure amassed was used to distinguish frequent attenders (FA) from non-frequent attenders. As a result, frequent attenders were defined as those who had participated in more than twelve consultations during the study year. Various reputable publications have utilized similar classification methods, allowing for a comparison of results to be made^[9,16,17].

Data Collection

The study design can be differentiated into two components. The first one was a descriptive study in which frequency of attendance from January to December 2003 inclusively was evaluated by reviewing the electronic database of the center.

The second component of the study was a case-control, which aimed to identify the main factors that influenced the frequency of attendance. Using the computerized database of the structure, all patients that attended the clinic during 2003 were listed. Frequent and non-frequent attenders (NFAs) were identified. For the purpose of comparison, 400 FA and a similar number of NFAs (control group), were selected randomly. Selected subjects were recalled for a structured interview and their records were reviewed manually for extraction of the required information.

Data abstracting were performed by trained staff using a data collection form which included information regarding any history of chronic illness, information about the last consultation and socio-demographic data, which was obtained from information already noted in patients' records. Data regarding the last consultation requested by the patient was analyzed, where the most significant complaint of the patient was considered. An inquiry about the presence of a chronic illness was made, as well as whether the chronic illness was under control or not. Patients were labeled as uncontrolled hypertensives if the mean of the last three measurements of systolic blood pressure was ≥ 140 mmHg and / or diastolic blood pressure was ≥ 90 mmHg. Patients were labeled as uncontrolled diabetics if the mean of the last three measurements of fasting blood sugar was ≥ 6.1 mmol/l. Other chronic diseases were considered as controlled, if patient was under medical supervision (treatment or specific regimen) and presented with normal figures during examination and / or investigation.

Patients were excluded from the study if they had a terminal disease or severe mental illness or they were pregnant during 2003. Also, patients who died during the study period were not included.

Collected data were sent to the Department of Health and Vital Statistics, Ministry of Health for processing and analysis.

Sample size:

Assuming that a hypothetical factor (e.g. presence of chronic illness) has a prevalence in the control subjects of 10% and is associated with an Odds Ratio equal to two or more, the number of cases required is 286 (with $\alpha = 0.05$ and $1 - \beta = 0.90$), with a similar number of subjects as controls^[18]. Thus the actual sample size of 400 cases would allow for reliable detection of risk factors which might have a prevalence varying more than 10% from the control group. Also, this would allow facing an expected non-response of recalled subjects of 25%.

Statistical analysis

The median was used to fulfill the descriptive

purpose of quantitative variables. For the case-control study, analyses were initially carried out to compare between FA and NFA groups based on a series of bi-variate comparisons. Differences between groups were detected by Chi square test for qualitative variables and Mann-Whitney test for quantitative variables.

For the possible confounding effect of the variables, multiple logistic regressions were used for the final analysis to predict factors which may contribute to frequent attendance (the main outcome of interest). In multivariate analysis, the associations between exposures and outcome were expressed in terms of odds ratios (OR) together with 95% confidence intervals (95% CI)^[19].

All the explanatory variables included in the logistic model were categorized into two or more levels (^R=reference category): Age (years): <30^(R), 30-39, 40-49, 50-59, ≥60; Sex: Male^(R), female; Nationality: Kuwaiti^(R), non-Kuwaiti; Marital status: Single^(R), married, divorced / widowed; Number of children: None^(R), 1-3, 4-6, ≥7; Education: Primary or less^(R), intermediate, secondary, high; Occupation: Not working^(R), manual, clerical, professional, student; Job type: Governmental^(R), non-governmental, others; Chronic illness: None^(R), yes controlled, yes uncontrolled. Standardization of age and sex had not been considered as it was preferred to enter them as covariates in the multivariate logistic model. Analysis was performed using Statistical Package for Social Sciences "SPSS-11 for Windows".

RESULTS

During 2003, a total number of 16,068 patients made 77,970 visits to the practice under the study. Out of them, 932 FAs made 14,970 visits. In other words, 5.8% of patients were responsible for 19.2% of the total number of visits. Overall, the median number of visits per patient in a single year was five. The median number of visits per FA patient was 16, whilst it was only four visits for NFA.

Socio-demographic details, the presence of chronic illness, together with the results of bivariate analyses are shown in Tables 1 and 2. The results of the bivariate analyses revealed that age, sex, nationality, marital status, number of children, occupation were significantly associated with frequent attendance ($p < 0.001$). The median age for FAs was 47 years compared 28.3 years in NFAs. Frequent attendance increased among older age groups and women. Females outnumbered males in all age groups except ≥ 60 years. After the age of sixty, more FAs were seen among males as compared to females (as seen in Fig. 1). Also, chronic illnesses, except skin diseases, were significantly associated with FA phenomenon.

Table 1: General characteristics of frequent attenders (372 cases) and non-frequent attenders (368 controls)

Variables	NFA (n = 368)		FA (n = 372)		p*Value
	n	%	n	%	
Age:					
< 30	100	27.4	55	14.8	< 0.001
30 -	93	25.5	57	15.3	
40 -	97	26.6	84	22.6	
50 -	54	14.8	95	25.5	
≥ 60	21	5.8	81	21.8	
Sex:					
Male	145	39.4	100	26.9	< 0.001
Female	223	60.6	272	73.1	
Nationality:					
Non-Kuwaiti	135	36.7	33	8.9	< 0.001
Kuwaiti	233	63.3	339	91.1	
Marital status:					
Single	97	26.4	52	14.0	< 0.001
Married	260	70.7	284	76.3	
Widowed / divorced	11	3.0	36	9.7	
Number of children:					
None	138	37.5	86	23.1	< 0.001
1 - 3	120	32.6	76	20.4	
4 - 6	93	25.3	159	42.7	
≥ 7	17	4.6	51	13.7	
Education:					
Primary or less	86	23.4	80	21.5	0.07
Intermediate	44	12.0	55	14.8	
Secondary	86	23.4	111	29.8	
High	152	41.3	126	33.9	
Occupation:					
None	102	27.7	184	49.5	< 0.001
Manual	114	31.0	33	8.9	
Clerical	74	20.1	88	23.7	
Professional	56	15.2	59	15.9	
Student	22	6.0	8	2.2	
Working hours / day[#]:					
< 6	13	4.9	23	12.2	< 0.001
6 - 8	170	63.9	145	77.1	
≥ 9	83	31.2	20	10.6	
Type of job:					
Governmental	118	32.1	146	39.2	< 0.001
Non governmental	126	34.2	34	9.1	
Others ^{\$}	124	33.7	192	51.6	

NFA: Non-frequent attenders.

FA : Frequent attenders.

*: Chi square test was used except for age, number of children and working hours where Mann-Whitney test was used; #: Not working subjects were excluded; \$: Not working subjects and students

Non-Kuwaitis represented 36.7% of NFAs and only 8.9% of FAs. The total number of non-Kuwaitis (cases and controls) in this study was 168, among whom 122 were manual workers. Out of these workers, 114 patients were non-governmental employees who constituted 18 FAs and 96 NFAs.

A look at the general characteristics of the last visit to the clinic made by the subjects of the study showed that only 45.5% of FAs presented with specific symptoms whilst 17.7% and 18.3% attended for repeat medical prescriptions and regular check-ups respectively. The corresponding figures in

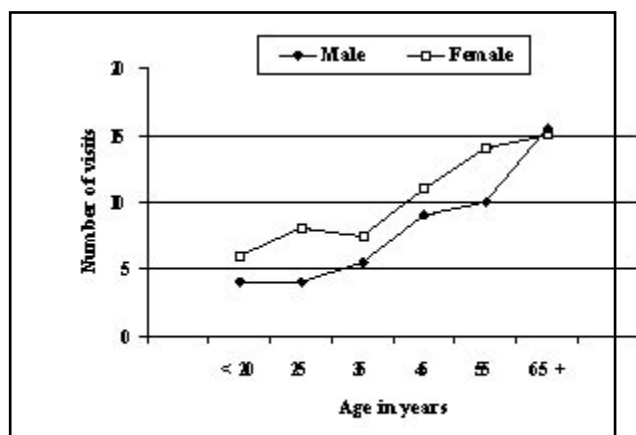


Fig 1: Median number of consultations per 12 months made by patients

NFA were 67.9%, 10.3% and 11.7% ($p < 0.001$). No significant difference regarding the type of symptoms in the two groups was detected. Chronic diseases were by far more frequent in FA than in NFA ($p < 0.001$) (Table 3).

Table 4 summarizes the results of multiple logistic regression analysis which predicted determinants of FA. Overall, frequent attendance was more encountered among Kuwaitis than among non-Kuwaitis (OR = 4.2, 95% CI: 2.3 – 7.9). Also it was more encountered amongst females (OR = 1.7, 95% CI: 1.2 – 2.5) and age groups “50 –” and “ ≥ 60 ” as compared with those less than 30 years (OR = 2.0, 95% CI: 1.1 – 3.5) and (OR = 3.7, 95% CI: 1.7 – 7.8) respectively. Non-governmental employees were less liable to be FAs (OR = 0.3, 95% CI: 0.2 – 0.6). Patients with chronic illness, either controlled (OR = 2.7, 95% CI: 1.8 – 4.1) or uncontrolled (OR = 4.1, 95% CI: 2.4 – 6.8) were more liable to be FAs as compared to attenders free from chronic diseases. Among Kuwaitis, persons with non-governmental jobs are less liable to be FAs (OR = 0.3, 95% CI: 0.2 – 0.6). Presence of controlled or uncontrolled chronic illness were common predictor variables in both Kuwaiti (OR = 2.3, 95% CI: 1.9 – 4.2), (OR = 4.7, 95% CI: 2.7 – 8.3) and non-Kuwaiti (OR = 7.0, 95% CI: 2.5 – 19.6), (OR = 7.2, 95% CI: 2.5 – 20.7) groups respectively.

DISCUSSION

Frequent attendance to primary health care centers is an issue that needs to be addressed as it can potentially be a waste of valuable resources, especially time, leading to long waiting lists and a fall in the quality of a physician's performance. This study showed that 5.8% of patients were FAs who made 19.2% of visits to the SFPC during the study year. A possible explanation of this situation in Kuwait could be found based on the family physician's position in the health care system and health care regulations which may have influence

Table 2: Proportion of chronic illness among frequent attenders (372 cases) and non-frequent attenders (368 controls)

Chronic illness	NFA (n = 368)		FA (n = 372)		p*Value
	n	%	n	%	
Hypertension	71	19.3	160	43.0	< 0.001
Cardio-vascular diseases	16	4.3	53	14.2	< 0.001
Diabetes mellitus	55	14.9	133	35.8	< 0.001
Urinary tract disorders	1	0.3	9	2.4	0.01
Bronchial Asthma	24	6.5	57	15.3	< 0.001
Skin diseases	8	2.2	4	1.1	0.24
Gastrointestinal diseases	7	1.9	28	7.5	< 0.001
Psychological disorders	2	0.5	9	2.4	0.04
Musculo-skeletal diseases	3	0.8	29	7.8	< 0.001

*: Chi square test

NFA: Non-frequent attenders

FA: Frequent attenders

on the number of visits. Also, the cost of frequent health seeking behaviour is relatively low, as medical services are free and easily available. As in many other countries, patients who need specialist healthcare must be referred from family practice center^[20]. Thus, FAs would consume health care on two levels (primary and secondary), undergo more unnecessary specialist examinations and receive more unnecessary prescriptions which all increases the number of visits to family practice office^[2,10].

Our results are consistent with the results from other studies which have used similar criteria for defining FAs. The Fourth National Survey of Morbidity and General Practice (MSGP4), carried out in the UK in 1995 showed that the most frequently consulting patients were 4.7% and they used 21% of consultations over one year^[21]. A similar study was carried in Croatia which showed that 23% of patients were FA and made 60% of visits^[7]. In Slovenia, FA constituted 24% of the total number of patients and made 54.8% of visits^[9]. Similarly, 20% and 25% of FAs in England and Finland made 50 and 55% of visits respectively^[3,8].

In this study, the median number of visits per patient was five. The corresponding number in Croatia, the Netherlands and Japan was 4.1, 5.7 and 5.6 respectively^[10,22]. Accordingly, the phenomenon of frequent attendance is present in Kuwait as in most other countries.

The results of this study show a significant difference between FA and NFA groups regarding the cause of last attendance. A lower proportion of symptomatic patients and higher percentage of patients who attended for medical prescriptions and periodic check-ups was found in FAs as opposed in NFAs. These results are in concordance with those of Browne, *et al* who identified high prescribing

Table 3: Reason for the last visit, complaint and type of the diseases among frequent attenders and non-frequent attenders

Variables	NFA		FA		p*Value
	n	%	n	%	
Main reason for the last visit:					
Check-up	43	11.7	68	18.3	< 0.001
Medicine prescription	38	10.3	66	17.7	
Presence of symptoms	250	67.9	169	45.5	
Others	37	10.1	69	18.5	
Total	368	100.0	372	100.0	
Main complaint:					
Pain	122	45.9	113	51.8	0.18
Fever	32	12.0	14	6.4	
Others	91	34.2	74	34.0	
Unexplained	21	7.9	17	7.8	
Total	266	100.0	218	100.0	
Type of the disease:					
Acute	187	62.8	114	35.0	< 0.001
Chronic	111	37.2	212	65.0	
Total	298	100.0	326	100.0	

*: Chi square test

NFA: Non-frequent attenders

FA: Frequent attenders

rates among a number of occasions associated with frequent attendance^[23]. This is a particular issue in Kuwait, as no more than a month's supply of medications can be prescribed by a doctor working in a governmental institution.

Multivariate analysis revealed that a variety of socio-demographic factors and chronic illness can strongly predict if a patient is destined to become a FA. There were more FAs among older age groups and women, a finding which is similar to that of other studies^[4,10,24]. Some studies have even established that high attendance rates are prevalent amongst elderly women specifically^[11,24,25]. The number of women amongst FAs was particularly marked in the below fifty years age group.

The predominance of women and senior consulters is a universal phenomenon. Women of this age are often both wage-earners and have great responsibility for care of their family. Duplication of work and the role of women in society is a possible cause of their higher morbidity^[26,27]. Women were thought to be more willing to report symptoms and feelings and being more familiar with the staff and setting^[6]. Although, it is also possible that elderly women represent a significant proportion of FAs as they tend to have a longer life expectancy. Older age is associated with an array of health problems and thus senior citizens constitute a large proportion of visitors.

There was a vast difference in the number Kuwaitis and non-Kuwaitis attending the clinic. Kuwaiti patients are 4.2 times more liable to be FAs

Table 4: Factors associated with frequent attendance in general practice: result of multivariate logistic analysis

	Overall		Kuwaiti	Non-Kuwaiti
Variable	OR	95% CI	OR 95%CI	OR 95% CI
Nationality:				
Non-Kuwaiti ^(R)	1		---	---
Kuwaiti	4.2	(2.3 – 7.9)		
Sex:				
Male ^(R)	1		NS	NS
Female	1.7	(1.2 – 2.5)		
Age:				
< 30 ^(R)	1			
30 –	1.0	(0.6– 1.7)	NS	NS
40 –	1.2	(0.7– 2.0)		
50 -	2.0	(1.1 – 3.5)		
≥ 60	3.7	(1.7 – 7.8)		
Type of job:				
Governmental ^(R)	1		1 (0.2 – 0.9)	NS
Non governmental	0.3	(0.2 – 0.6)	0.4 (0.4 – 0.9)	
Others \$	0.5	(0.3 – 0.7)	0.6	
Chronic illness			(1.9 – 4.2)	
None ^(R)	1		1 (2.7 – 8.3)	1
Yes controlled	2.7	(1.8 – 4.1)	2.3	7.0 (2.5 – 19.6)
Yes uncontrolled	4.1	(2.4 – 6.8)	4.7	7.2 (2.5 – 20.7)

^(R) = reference category ; NS = Non significant; OR = odds ratio

CI = confidence interval

\$: Not working subjects and students.

Variables included in the models: Age, sex, nationality, marital status, number of children, education, occupation, type of job and presence of chronic illness

as compared with non-Kuwaitis. Another finding which may be correlated with nationality is that non-governmental employees were less prone to be FAs. Due to these results, together with the finding that non-governmental, non-Kuwaiti, manual workers are mostly NFAs (84.2%), a multivariate analysis model was conducted for each of the Kuwaiti and non-Kuwaiti patients. This revealed that the presence of chronic illness was the only predictor of frequent attendance among non-Kuwaitis. This is probably due to the fact that health care is free for Kuwaiti citizens, whereas non-Kuwaitis pay health insurance and a fee depending on the procedure. Also, the fact that non-Kuwaiti inhabitants of Al-Surra area are mostly non-governmental manual workers explained that this category of low income subjects did not attend the practice unless they had disease manifestations. In addition, these subjects are mostly middle-aged and healthy. All these factors would influence the rate of attendance, especially the financial consequences, as most immigrant workers tend to go back home when diagnosed with a chronic illness.

Thus it can be hypothesized that an introduction of similar fees to Kuwaiti would be a deterrent to high consultation rates, though they would be unacceptable. A better approach is to provide a balance between easy access to health care and insuring that it is not taken for granted by making it

clear when it is appropriate to see a physician.

Chronic diseases, such as hypertension, cardiovascular and diabetes were by far more encountered in FA (69.4%) than in NFA (34.8%). Patients with long-term conditions had high risk of frequent attendance, especially those with uncontrolled diseases who needed frequent follow-up visits and presented the necessary and proper aspects of frequent attendance phenomenon. In fact, the decisive factor for frequent visits was not severity of chronic disease, but administrative and social requirements imposed on the physician and chronically ill patient. In other words, most of these consultations are physician initiated as part of planned follow-up. However, patient usually assesses his or her condition as more serious than the physician does^[28]. As chronic physical illness appeared to be a major factor, perhaps a better strategy for chronic disease management will relieve the problem of unnecessary frequent attendance^[11].

Conversely, frequent attendance can be viewed as an indicator of better healthcare, as patients with chronic illnesses, whose management is often difficult and compliance to treatment is poor receive more support and care from physicians.

Kuwait had 1.6 physicians per 1000 population in 2003, which is one of the highest rates in the region and is greater than that in some developed countries^[29]. Our opinion is that it is necessary to introduce better managerial strategies that filter out unnecessary consultations. Unfortunately, we did not have opportunity to examine physician factors although several factors related to the physician may influence the attendance rate^[2,3]. It was suggested that the general practitioner plays a role in the initiation, maintenance and course of frequent attendance in general practice^[25]. Also, psychiatric profile of FA needs to be studied. Several studies have shown that FA in primary health have high rates of psychiatric disorder in comparison with normal attenders^[30].

Although the study was carried out in a single practice, the general characteristics of the practice and the study population shared many features of all health structures available in all residential areas in Kuwait. However, a multi-centric study of all factors associated with frequent attendance to primary health practice including patient beliefs and perceptions of health and health services as well as an examination of physician- patient relationship is recommended.

CONCLUSIONS

Chronic illnesses mostly dictate high consulting attendance. Also, socio-demographic factors, especially nationality, gender, age, occupation were indicators of frequent attendance in general

practice. The phenomenon of frequent attendance is present in Kuwait as in most other countries. Further investigations would reveal more about the causation of frequent attendance and whether it is a problem that requires the attention of health systems regulators.

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Original Article

Patient Satisfaction with Primary Health Care Services in Kuwait

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ABSTRACT

Objectives: To evaluate patient satisfaction with respect to primary health care (PHC) services in Kuwait.

Design: A cross sectional sample survey conducted from November 2003 to February 2004.

Setting: PHC centers, Kuwait.

Subjects: A total of 1255 Kuwaiti patients, 16 years of age and above attending selected PHC centers.

Intervention: A self administered Arabic language questionnaire with two components, the socio-demographic characteristics and overall satisfaction rating with particular services in the selected PHC centers, was generated and used.

Main Outcome Measure(s): Patient's satisfaction with respect to PHC services, consultation skills and nursing care.

Results: Overall satisfaction was 60.7%. Females were

more satisfied than males, and elder age group more satisfied than middle-and young-age groups. 59% rated receptionist's care excellent and 47% rated physician's consultation skills excellent. The main dissatisfaction from services was about discontinuity of care; only 30.0% admitted their ability to see their regular physician always and 33.0%, sometimes. Only 31% reported the care given by practice nurse as excellent.

Conclusion: Although patients are satisfied with PHC services in Kuwait, areas such as: physicians rendering more attention to the patient's beliefs, anxieties, and opinion regarding the management plan, skill training to physicians for better communication and practice nurse services require more improvement. Setting standard target for all services and encouraging all PHC providers to achieve these targets is also recommended.

KEYWORDS: communication skills, Kuwait, nurse, physician, primary health care, satisfaction

INTRODUCTION

Primary Health Care (PHC) service is the most frequently used in any health care system. It is defined by the World Health Organisation (WHO) as essential health care made universally accessible to individuals and families in any community by means acceptable to them. The objective of primary health care is to deliver integrated health care services for the population^[1]. Patient satisfaction surveys have a long history in the assessment of consultations and patterns of communication and are amongst the best means of assessing the interpersonal aspect of care^[2]. It is defined as "an evaluation based on the fulfilment of expectations". Evaluation of patient satisfaction has become a standard part of evaluation of a health care system, and meeting patient expectations has become one of the main objectives of health care providers^[3]. The importance of meeting the expectations of the population by health care providers is widely accepted as one of the indicators of a functioning system^[4]. It is becoming increasingly recognised that patient's views should

be taken into account as a part of comprehensive assessment of quality of care^[5]. Satisfied patients are more likely than dissatisfied ones to continue using health care services, maintain their relationships with specific health care providers and comply with care regimens^[3]. Patient satisfaction can be utilised for three main purposes, first: as an evaluation of quality of care, second: as an outcome variable in its own right and third: as an indicator of weaknesses in service that is in a process of change^[6].

Assessment of patient satisfaction offers a way of optimising health status and prevents waste of medical resources. It is a systematic and permanent process that should be integrated and implemented effectively in the everyday work of all health care system members. The aim of this study was to evaluate satisfaction levels of the Kuwaiti patients with regard to selected PHC services in Kuwait.

SUBJECTS AND METHODS

One-thousand two-hundred fifty-five patients attending 15 PHCs participated in this survey

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conducted in Kuwait during the period from November 2003 to February 2004.

The target population was obtained from the PHCs including all Kuwait governorates. The health centers were selected randomly using random tables and the number of practices selected was almost 20% of the total population of that governorate. The criteria for selection was any Kuwaiti patient aged 16 years and above registered in the same health center area and who had visited the health center more than twice to enable him to evaluate the services precisely. He should have visited the health center for any reason and must be willing to participate and complete the questionnaire before and not after consultation, because the aim was to evaluate the services not for this visit only but for all previous visits. All participants were informed that the purpose of the study was to evaluate and assess their satisfaction as regards the PHC services.

Patients were assured that questionnaires will not be seen by their physicians. We decided with the receptionist to select every seventh patient satisfying the required criteria for contribution. Verbal consent was taken and those who refused participation were excluded. Data were collected via a self-administered pilot tested questionnaire which included socio-demographic information as well questions related to the overall and thorough satisfaction with the services. The questionnaire used was developed by a group of family physicians guided by the questionnaire of General Practice Assessment Survey (GPAS)^[7]. We preferred not to use the GPAS questionnaire itself as being a long questionnaire; it would affect the response rate. Besides, some points in the GPAS questionnaire were not appropriate for the PHC system in Kuwait. The points selected were the socio-demographic characteristics, the access, the receptionist, continuity of care, physician's communication skills, practice nurse care plus overall and thorough satisfaction with the health care services in the selected health centers. A four and sometimes five point rating scale was used to elicit the opinion from the patients (poor, fair, good and excellent or poor, fair, good, excellent and I don't know).

A total of 1314 questionnaires were collected out of which 59 were rejected because they were incomplete. The total number of completed questionnaires was 1255 and the response rate was 76%. SPSS software version 11 was used for the analysis of the data. Chi-square test was used to compare between two variables. A p-value of < 0.05 was considered as a cut off point for significance.

RESULTS

The results revealed that among the 1255 participants, 47.3% were male and 52.7% were

Table 1: Overall satisfaction according to patient's demographic variables

Variables	Total n (%)	Satisfied n (%)	Dissatisfied n (%)	Neutral n (%)	*p-value
Sex					
Male	594 (47)	354 (59.5)	171 (28.7)	69 (11.6)	NS
Female	661 (52)	409 (61.8)	180 (27.2)	72 (10.9)	
Age					
16-40	827 (65.8)	501 (61.0)	229 (28.0)	97 (12.0)	NS
> 40-60	392 (31.2)	238 (61.0)	114 (29.0)	40 (10.0)	
> 60	36 (2.8)	24 (67.0)	8 (22.0)	4 (11.0)	
Job					
Working	851 (67.8)	493 (58.0)	272 (32.0)	86 (10.0)	< 0.001
Not working	242 (19.3)	159 (66.0)	54 (22.0)	29 (12.0)	
Retired	162 (12.9)	111 (69.0)	25 (15.0)	26 (16.0)	
Education					
Primary & middle school	138 (11.0)	86 (58.0)	39 (26.0)	24 (16.0)	< 0.001
High school	550 (43.8)	308 (56.0)	170 (31.0)	72 (13.0)	
University	556 (44.3)	369 (66.0)	142 (26.0)	45 (8.0)	

* Chi-square test

female. 65.9% of the participants were from the 16-40 age group, 31.2% between 40 – 60 years and only 2.9% were > 60 years. The overall satisfaction rate for PHC services was 59.5% and 61.8% among male and female patients respectively. Although satisfaction was almost the same among the three age group, it was the highest among the elderly age group (67.0%). It was also the highest among the retired population (69.0%) and those with university or higher degree of education (66.0%). Table 1 profiles the socio-demographic characteristics and the overall satisfaction among them.

Table 2 shows the results of different services studied in this survey. As regards the evaluation for the waiting time before consultation begins, 25.0% consider it excellent and 26.0% consider it poor. Regarding the care offered by receptionists 58.7% considered it excellent. The overall satisfaction rate was 60.7%. 27.9% were dissatisfied.

Regarding satisfaction with physicians' consultation skills, 30.0% declared that they are always able to see their doctor whenever they want, 47.0% declared that their doctor asked thoroughly about their symptoms, 51.0% also found him to be an excellent listener and 49.0% found that their doctor explained their problem and treatment at the end of consultation. Tables 3 and 4 show the evaluation results of physician's consultation skills. Evaluation of practice nurse services showed that only 31.0% of the patients found that the quality of care offered by nurses was excellent. Table 4 shows the evaluation of the practice nurse care.

DISCUSSION

The measurement of patient satisfaction has

Table 2: Evaluation of patient satisfaction with respect to primary health care services

Variables	Total n (%)	Male n (%)	Female n (%)	p-value
How do you rate the convenience of your practice location?				
Poor	150 (12.0)	67 (11.3)	83 (12.6)	< 0.05
Fair	229 (18.0)	101 (17.0)	128 (19.4)	
Good	465 (37.0)	248 (41.8)	217 (32.8)	
Excellent	411 (33.0)	178 (30.0)	233 (35.2)	
How long do you usually have to wait until your consultation begins?				
10 minutes or less	510 (41.0)	235 (39.6)	275 (41.6)	NS
10-20 minutes	322 (26.0)	154 (25.9)	168 (25.4)	
20- 45 minutes	321 (26.0)	157 (26.4)	164 (24.8)	
> 45 minutes	102 (8.0)	48 (8.1)	54 (8.2)	
How do you rate the waiting time before consultation?				
Poor	330 (26.0)	146 (24.6)	184 (27.8)	NS
Fair	348 (28.0)	157 (26.4)	191 (28.9)	
Good	259 (21.0)	138 (23.2)	121 (18.3)	
Excellent	318 (25.0)	153 (25.8)	165 (25.0)	
How do you rate the ability to get through in to the practice on the phone?				
Poor	227 (18.0)	131 (22.1)	96 (14.5)	< 0.05
Fair	166 (13.0)	75 (12.6)	91 (13.8)	
Good	125 (10.0)	54 (9.1)	71 (10.7)	
Excellent	163 (13.0)	63 (10.6)	100 (15.1)	
Don't know	574 (46.0)	271 (45.6)	303 (45.8)	
If you want to see a particular doctor how quickly do you usually see him?				
Same or next day	891 (71.0)	419 (70.5)	472 (71.4)	NS
Within 2-3 days	202 (16.0)	103 (17.3)	99 (15.0)	
After 4 days or more	25 (2.0)	12 (2.0)	13 (2.0)	
Don't Know	137 (11.0)	60 (10.1)	77 (11.6)	
If you need to see a GP urgently, can you normally get seen on the same day?				
Yes	729 (58.0)	360 (60.6)	369 (55.8)	< 0.05
No	178 (14.0)	69 (11.6)	109 (16.5)	
Don't know	348 (28.0)	165 (27.8)	183 (27.7)	
How do you rate the way you are treated by receptionists in your clinic?				
Poor	53 (4.2)	34 (5.7)	19 (2.9)	< 0.05
Fair	196 (15.6)	94 (15.8)	102 (15.4)	
Good	269 (21.4)	137 (23.1)	132 (20.0)	
Excellent	737 (58.7)	329 (55.3)	408 (61.7)	
Overall, how satisfied are you with your practice?				
Not satisfied	351 (27.9)	171 (28.7)	180 (27.2)	NS
Satisfied	763 (60.7)	354 (59.5)	409 (61.8)	
No comment	141 (11.2)	69 (11.6)	72 (10.8)	

become a common way to elicit patient's views about the health care delivered. This study is an effort to evaluate patient's satisfaction for a better patient focus. The overall satisfaction score in this study was 60.7% for all services. This result was compared to results of two other studies; one, assessing patient's satisfaction in Kuwait where the

Table 3: Patient satisfaction as regards physician's consultation skills in primary health care

Skills	Total n (%)	Male n (%)	Female n (%)	p-value
How often do you see your regular doctor?				
Always	377 (30.0)	189 (31.8)	188 (28.4)	NS
Usually	349 (28.0)	147 (24.7)	202 (30.6)	
Sometimes	410 (33.0)	203 (34.2)	207 (31.3)	
Rarely	119 (9.0)	55 (9.3)	64 (9.7)	
How thoroughly does your doctor ask about your symptoms?				
Poor	41 (9.0)	72 (12.1)	41 (6.2)	< 0.001
Fair	254 (20.0)	130 (21.9)	124 (18.8)	
Good	296 (24.0)	141 (23.7)	155 (23.4)	
Excellent	592 (47.0)	251 (42.3)	341 (51.6)	
How well the doctor listens to what you had to say?				
Poor	322 (26.0)	189 (31.8)	133 (20.1)	< 0.001
Fair	24 (2.0)	13 (2.2)	11 (1.7)	
Good	268 (21.0)	122 (20.5)	146 (22.1)	
Excellent	641 (51.0)	270 (45.5)	371 (56.1)	
How well the doctor explained your problems?				
Poor	120 (10.0)	76 (12.8)	44 (6.7)	< 0.001
Fair	256 (20.0)	126 (21.2)	130 (19.7)	
Good	261 (21.0)	135 (20.5)	126 (19.1)	
Excellent	618 (49.0)	257 (43.3)	361 (54.6)	

overall satisfaction rate was 62.0%, and the other done in Saudi Arabia where the overall satisfaction rate was 49.0%^[1,8].

Socio-demographic characteristics of patients as a significant factor in evaluating patient satisfaction with health care services in general have been researched in many studies. In this study, patient's age, occupation and educational level were more consistently correlating variables than gender. The study concluded that older age group were more satisfied with the services than the young or middle age group. This could be due to higher morbidity and consulting rates among older patients which means that this group may have more contact with PHC services and thus have more opportunity to be favourably influenced by the services provided. This finding was similar to findings of other studies in which the satisfaction was more among the old age groups^[1,9-12]. We noticed that the satisfaction among the young age group was more in females than males, while in the middle age group, males showed more satisfaction than females. Among the old age group, males and females were nearly equally satisfied. In our study, although generally females show more satisfaction than males, they are both nearly equally satisfied with the services. This result is similar to results of other studies^[1,13].

Table 4: Patient's satisfaction as regards practice nurse services in primary health care

Skills	Total n (%)	Male	Female n (%)	p-value n (%)
Have you seen a nurse from your practice in the last 12 months?				
Yes	856 (68.0)	433 (72.9)	423 (64.0)	< 0.001
No	399 (32.0)	161 (27.1)	238 (36.0)	
How many times have you seen a nurse from your practice in the past 12 months?				
1-2 times	358 (29.0)	165 (27.8)	193 (29.2)	< 0.05
3-4 times	317 (25.0)	166 (27.9)	151 (22.8)	
≥ 5 times	164 (13.0)	92 (15.5)	72 (10.9)	
Don't know	416 (33.0)	171 (28.8)	245 (37.1)	
How well does the nurse listen to what you say?				
Poor	61 (5.0)	32 (5.4)	29 (4.4)	< 0.05
Fair	215 (17.0)	112 (18.9)	103 (15.6)	
Good	209 (17.0)	105 (17.7)	104 (15.7)	
Excellent	365 (29.0)	183 (30.8)	182 (27.5)	
Don't know	405 (32.0)	162 (27.3)	243 (36.8)	
How do you rate the quality of care they provide?				
Poor	147 (12.0)	74 (12.5)	73 (11.0)	< 0.05
Fair	192 (15.0)	102 (17.2)	90 (13.6)	
Good	125 (10.0)	65 (10.9)	60 (9.1)	
Excellent	391 (31.0)	191 (32.2)	200 (30.3)	
Don't know	400 (32.0)	162 (27.3)	238 (36.0)	
How well do they explain your health problem?				
Poor	45 (4.0)	20 (3.4)	25 (3.8)	< 0.05
Fair	169 (13.0)	86 (14.5)	83 (12.6)	
Good	66 (3.0)	34 (5.7)	32 (4.8)	
Excellent	540 (43.0)	277 (46.6)	263 (39.8)	
Don't know	435 (35.0)	177 (29.8)	258 (39.0)	

As regards occupation, it was seen that retired patients showed higher satisfaction whereas those in service were least satisfied. This is similar to findings in another study^[14] and this could be due to the fact that working patients may sometimes not achieve their objective during consultation, especially if the reason for consultation was to get a sick leave from work and they are confronted with physician's refusal to sign unreasonable sick leaves leading to a conflict in physician - patient communication and relationship. In Kuwait, we as physicians are aware about the magnitude of this problem. We also noticed that satisfaction was more among those with high school and university degree of education. This finding is supported by another study^[14].

Although a general question about services at the primary health care indicated good level of satisfaction from participants, the level of satisfaction was invariably less when specific items of PHC were considered. One of the items evaluated in this survey was access and the convenience of the clinic location; the results demonstrate that

the majority of participants were satisfied with the location of their clinic. Regarding how quickly they can see a specific physician if they need that, the majority response was on the same day or next day. Regarding the evaluation of waiting time, patients were moderately satisfied with the waiting time before consultation. Patients are more likely to be satisfied when they do not wait too long and this result is comparable to results of other studies^[15,16]. About the ability to contact the clinic by phone, most patients were unable to evaluate as they had not tried it. As regards evaluation of access in case of emergency and the possibility of being seen on the same day, 58% of patients thought they could see a general physician on the same day. This result was surprising as we expected higher rates of satisfaction regarding this service simply because in Kuwait there is no appointment system in PHC and any patient can be seen at any time even without an emergency.

The co-operation of the receptionists in the health center was also evaluated. The results showed that majority of the participants were satisfied with the receptionist's care and co-operation during their visit to the health center. Thus, receptionist's care is a good predictor for patient's satisfaction in PHC in Kuwait. However, results of a study done Saudi Arabia showed that the majority of PHC patients were dissatisfied from receptionist services^[8].

Continuation of care is one of the most significant points for evaluation in PHC; patients expect to see their physician at each consultation to ensure the continuation of care, and they are disappointed if they are not able to see their usual physician during their visit. In this survey, only 30% of the patients were able to see their usual physician always and 27.8% admitted that they were able to see their physician most of the time. Although this result is similar to that from another study^[17], it is still undesirable. We have to admit that physician's responsibilities are sometimes complicated to a level that he is unable to be available for his patients all the time. In our opinion, the best way out for this problem is to apply the appointment system in PHC for non-emergency cases. This will limit the size of the problem giving better chance for both the patient and the physician to meet each other more frequently.

Physician's consultation skills are considered to be the core of patient satisfaction, not only in PHC but also in secondary health care. Although there are many areas that need evaluation, in this study we decided to evaluate the consultation skills. We chose communication skills such as history taking, listening to patients attentively, and explaining to them about their health problems as these factors significantly influence the degree of satisfaction.

The results demonstrate that the majority of patients agreed that physicians asked about their symptoms thoroughly, listened to them and explained their problems well. Patients expect from their physician an explanation of what is happening to them; they want to feel that their physician understands their problem. Patient's dissatisfaction with the consultation skills is a multi-factorial problem. Either the physician lacks appropriate communication and knowledge skills or the patient comes with unrealistic expectations. Since the PHC system is free of charge for Kuwaiti patients, this encourages the patients to come frequently for minor problems, leading to crowded clinics and lack of enough time for each patient. In this opinion, the presence of certain amount of disagreement between the physician and his patient due to their different expectations and experiences is inevitable and it would be unrealistic to expect a total absence of conflict between them. This study has shown that physician's communication skills and the time spent in talking, listening, explaining and offering enough space to answer their queries and relieve their anxieties were strong and important correlates of patient's satisfaction. This result is in agreement with that from another study^[18].

As regards practice nurse services, our study showed that patients were not very satisfied (with reference to listening to patients, quality of care given to them and explanations offered). This result was similar to the finding of another study^[19]. In our opinion, this result is the outcome of the Ministry of Health regulations through which nurses in PHC are not able to use their skills fully even if they are highly skilful. There are limitations to their responsibilities, especially as regards communication with patients. We believe that there should be a drastic change regarding practice nurse services in PHC in Kuwait. The decision makers in the Ministry of Health should review these regulations giving the PHC nurses more responsibilities, training them in new skills, encouraging them and trusting their abilities. Patient satisfaction surveys are in many ways an inactive rather than active form of participation and are fraught with difficulties^[20]. Nevertheless, such surveys yield valuable but variable information. The results show many areas in which quality improvement is required.

CONCLUSION

This survey concluded that no one factor alone could provide satisfaction with primary health services in Kuwait.

There is a need for corrective intervention in some services such as the waiting time for consultation and the continuity of care. Better services can be

offered by increasing the numbers of clinics and applying the appointment system in PHC centers, principally for chronic diseases.

Attention should be given to the duties of the practice nurses. They should be encouraged to take more responsibilities and to increase both their knowledge and communication skills and to recognize patients' anxieties and needs.

General physicians should be aware of the important predictors for patient satisfaction; they might themselves pay more attention to their patient's opinions by asking patients through a questionnaire about their expectations and perceptions from consultation. It is of great benefit to introduce patient satisfaction studies in their practice group periodically.

Health care providers should put a standard target for all services and encourage all PHC providers to work hard to achieve this target.

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Original Article

Patient Satisfaction According to Type of Primary Healthcare Practitioner in the Capital Health Region, Kuwait

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ABSTRACT

Objectives: To evaluate patient satisfaction according to the type of primary healthcare practitioners (family medicine versus general practice physicians) and study the relationship between patients' socio-demographic characteristics and their level of satisfaction with primary healthcare services

Design: Cross-sectional questionnaire based survey

Setting: Four family medicine and four general primary care practice centers in the Capital Health Region in Kuwait

Subjects and Methods: Four hundred patients of 15-years-and-above age reporting to the selected centers. Data were collected through personal interview using a questionnaire that included socio-demographic characteristics of patients and practitioners.

Main Outcome Measure: Patient satisfaction was measured through 20 items using a five point Likert scale.

Results: In the family medicine setting, Kuwaiti

practitioners were prevalent (60%), while non-Kuwaiti practitioners were predominant in general practice (74%, $p < 0.001$). Old practitioners (50 years old and above) were more prevalent in general primary care than in family medicine setting ($p = 0.001$). The patients mean satisfaction score in family medicine (78.4%) was higher than that in general practice (75.2%). Females with higher income and with more follow up visits reported higher levels of satisfaction ($p = 0.013$, 0.02 , and 0.019 respectively). Patient satisfaction was not affected by gender, nationality or age of the treating practitioner in both practices

Conclusion: Patients attending family medicine clinics reported higher satisfaction than those attending general clinics. There is a need to remedy the areas that received low levels of patient satisfaction, and to continue the upgrading of the general and family medicine practitioners.

KEY WORDS: family practice centers, patient satisfaction, primary health care centers

INTRODUCTION

Studies of patient satisfaction towards health services, health personnel and resources constitute important elements in the extent to which health services received meet consumers' expectations and needs. They can be used as a means to assess the quality of health care provided. They also help providers to better understand consumers' views^[1].

A sustained partnership distinguishes the patient – physician relationships in primary care from other settings. These relationships are characterized by providing support and empathy, communication, mutual trust, and a physician's whole – person knowledge of the patient^[2].

Primary healthcare as a concept and strategy for providing community health services has

been accepted and adopted by many countries, particularly the developed ones. Affluent Gulf countries including Kuwait have established their healthcare systems where first contact comprehensive services are offered to all eligible individuals through a network of primary healthcare centers (PHCCs) serving defined catchment areas according to residence^[3].

The PHCCs have an important role in providing the basic healthcare services and in reducing the pressure on the secondary and tertiary healthcare facilities. Hence, if these PHCCs fail to provide satisfactory services to patients, this will lead to excessive utilization of emergency rooms in hospitals and adverse patients attitudes towards the healthcare system^[4].

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Patient satisfaction studies started to appear in the literature about half a century ago. With the growing awareness of the patient as an evaluator of healthcare, more sophisticated and specialized multidimensional scales for measurement of satisfaction were suggested^[3]. In Kuwait, such studies are scarce and are of a general nature. Medline search revealed only one study conducted in 2000 to determine factors affecting patient satisfaction with physician services in a primary healthcare center in Kuwait. It concluded that females, married, laborers and patients with higher income levels had the highest satisfaction scores. However this study did not take into consideration family medicine qualification of physicians nor their general characteristics^[1].

There is a difference in patient satisfaction according to type of practitioners attending (PHCCs) in Kuwait. Patients registered in family medicine (FM) clinics are hypothesized to be more satisfied than those attending the general practitioner (GP) clinics.

This study aims to evaluate patient satisfaction according to type of practitioners (FM versus GP) in primary healthcare practices in Kuwait and to study the relation between patient socio-demographic characteristics and level of their satisfaction with the primary healthcare services.

SUBJECTS AND METHODS

Setting:

Healthcare system in Kuwait is divided into five regional health authorities in the five governorates. Health services are provided at three levels. Primary healthcare is the first level and is provided by 77 PHCCs served by either FM practitioners in FM centers or GPs in primary healthcare or GP centers. The Capital health region, at the primary level, served about 474,600 inhabitants in 2005 with 184 physicians. They were classified into 58 FM physicians and 126 GPs. Kuwaitis represented 80% of FM qualified physicians and 32% of the other GPs. Females constituted 81% of FM physicians and 44% of the GPs^[5].

The present study design is a cross sectional survey conducted in the Capital health region from March to May 2005. Four FM centers (Keifan, Shameya, Surra, and Mansoriya) and four GP centers (Sulaybekhat, Adeliya, Nuzha, and Dae'a) were randomly selected for the study.

Subject identification and recruitment:

In each center, a sample of 50 patients was selected. Subjects were eligible for the study if they were 15 of age or older within the enrollment period. Every third patient was asked to participate in the study after obtaining his / her verbal consent, and

was assured of the anonymity and confidentiality of his / her responses. Data was collected through personal interview with patients who were chosen to participate using a structured questionnaire. The study sample included 461 patients. However, 61 (13.2%) of them refused to participate, due to shortage of time on their part, or they were too sick to be interviewed. Hence, data on 400 participants were used in the final analysis, with a response rate of 86.8%.

Research instrument:

The research instrument (questionnaire) items were selected from published patient satisfaction questionnaires^[6,7]. Selection of items was based on their relevance to the primary healthcare setting in Kuwait. It included two sections: 1) Socio-demographic characteristics, number of previous visits, and reasons for the current visit; and 2) A scale to measure patient's satisfaction which included 20 items about various areas desired in a clinical practice such as professional behavior of the treating practitioner, knowledge, clinical skills, doctor-patient communication, and technical aspects including the area of disease prevention. A five point Likert scale was used for each item with the extremes labeled "strongly disagree" scored 1 and "strongly agree" scored five. Scoring was reversed in five out of 20 items (Strongly Disagree 5, Disagree 4, Neutral 3, Agree 2, Strongly Agree 1) since these items were addressed in negative way. The highest percentages of participants were in the category "Agree" and in reversed items were in the category "Disagree".

Interviews were conducted in the healthcare center by the investigator immediately following the visit. The validity of the instrument was assured through translation of the original English version into Arabic and then independent back-translation into English. The questionnaire was pre-tested by administering it to 10 patients in various healthcare centers before preparing the final version in order to ascertain its clarity comprehended by participants and to estimate the time required for completing it. It was found that all items of the questionnaire were clear, and the average time required to complete it was between 5 - 8 minutes.

Statistical methods:

Coded data were keyed in the computer using the "Statistical Package for Social Science" (SPSS) software version 12.0 for windows (Chicago, Illinois, 2003). The value $p < 0.05$ was used as the cut-off level for statistical significance. Chi-square test was used to detect associations between categorical variables. Mann-Whitney test was used to detect significant difference between two groups regarding the number of visits and satisfaction score.

Table 1: Socio-demographic characteristics as reported by participants

Variable	Primary Healthcare Practitioner						p-value**
	Total (n = 400)		FM (n = 200)		GP (n = 200)		
	n	(%)	n	(%)	n	(%)	
Age (in years)							
< 30	143	(35.7)	68	(34.0)	75	(37.5)	0.43
30-49	196	(49.0)	97	(48.5)	99	(49.5)	
≥ 50	61	(15.0)	35	(17.5)	26	(13.0)	
Median (Min- Max)	35 (15 - 77)		36 (15 - 77)		33 (15 -70)		
Gender:							
Male	162	(40.5)	70	(35.0)	92	(46.0)	0.03
Female	238	(59.5)	130	(65.0)	108	(54.0)	
Marital status:							
Single	124	(31.0)	67	(33.5)	57	(28.5)	0.02
Married	258	(64.5)	119	(59.5)	139	(69.5)	
Divorced /Widowed	18	(4.5)	14	(7.0)	4	(2.0)	
Nationality:							
Kuwaiti	320	(80.0)	159	(79.5)	161	(80.5)	0.80
Non-Kuwaiti	80	(20.0)	41	(20.5)	39	(19.5)	
Educational level							
Illiterate	10	(2.5)	8	(4.0)	2	(1.0)	0.02
Elementary	14	(3.5)	9	(4.5)	5	(2.5)	
Intermediate/Secondary	211	(52.7)	92	(46.0)	119	(59.5)	
University and above	165	(41.3)	91	(45.5)	74	(37.0)	
Occupation:							
Unemployed*	184	(46.0)	94	(47.0)	90	(45.0)	< 0.001
Laborers	23	(5.8)	14	(7.0)	9	(4.5)	
Semi-skilled	84	(21.0)	29	(14.5)	55	(27.5)	
Skilled	14	(3.5)	2	(1.0)	12	(6.0)	
Semi-professional	68	(17.0)	45	(22.5)	23	(11.5)	
Professional	27	(6.8)	16	(8.0)	11	(5.5)	
Family income KD:							
< 500	76	(19.0)	41	(20.5)	35	(17.5)	0.01
500 -1000	138	(34.5)	54	(27.0)	84	(42.0)	
> 1000	186	(46.5)	105	(52.5)	81	(40.5)	
Type of visit:							
First	92	(23.0)	41	(20.5)	51	(25.5)	0.24
Follow-up	308	(77.0)	159	(79.5)	149	(74.5)	
Number of visits last year:							
Median (Min- Max)	6 (0 - 99)		7 (0 - 99)		6 (0 -97)		0.03\$

*Unemployed patients include students, housewives, and retired categories
 **p- values were generated from chi-square test; ^{\$}Mann-Whitney test was used; FM = Family Medicine; GP = General Practitioner

RESULTS

Socio-demographic characteristics of patients and practitioners:

Table 1 presents reported socio-demographic characteristics of the 400 participants in the patient

Table 2: Socio-demographic characteristics of the treating practitioners

Variable	Primary Healthcare Practitioner						p-value**
	Total (n = 400)		FM (n = 200)		GP (n = 200)		
	n	(%)	n	(%)	n	(%)	
Gender:							
Male	199	(49.8)	97	(48.5)	102	(51.0)	0.617
Female	201	(50.3)	103	(51.5)	98	(49.0)	
Nationality:							
Kuwaiti	172	(43.0)	120	(60.0)	52	(26.0)	< 0.001
Non-Kuwaiti	228	(57.0)	80	(40.0)	148	(74.0)	
Age (years):							
< 30	51	(12.8)	31	(15.5)	20	(10.0)	< 0.001
30-49	321	(80.3)	165	(82.5)	156	(78.0)	
> 50	28	(7.0)	4	(2.0)	24	(12.0)	

**Chi-square test; FM = Family Medicine; GP = General Practitioner

satisfaction study according to type of primary healthcare practitioner (FM or GP). Nearly half of participants (49%) were 30 - 49 years old with mean age equal to 36.2 ± 14.3 in FM and 33.4 ± 12.3 years in GP respectively ($p = 0.04$). Females were predominant in both settings, but were more prevalent in FM (65%) than in GP (54%) settings ($p = 0.03$). Two thirds of the participants (64.5%) were married, but a larger proportion consulted in GP (69.5%) than in FM (59.5%, $p = 0.02$). As the study was conducted in the capital governorate where most inhabitants were Kuwaitis, non-Kuwaiti patients represented only about one quarter of the participants in each setting. University graduates represented a higher proportion in FM (45.5%) than in GP setting (37%), while the participants with an intermediate level of education represented a higher segment (59.5%) in GP than in FM (46%) setting ($p = 0.02$).

There was a significant association between occupation and the type of primary healthcare setting ($p < 0.001$). Students, housewives, and retired patients (unemployed category) represented 46% of all participants, and they were nearly equally prevalent in FM (47%) and GP (45%) settings. Semi-professionals were more prevalent in FM (22.5%) than in GP (11.5%) while semi-skilled patients were more prevalent in GP (27.5%) than in FM (14.5%). There was a significant association between family income and type of primary healthcare setting ($p = 0.02$). Patients who reported family income exceeding KD 1000 constituted 46.5% of the participants, with a higher proportion of them in FM (52.5%) as compared to 40.5% in GP setting. The majority of participants reported for a follow-up

Table 3: Distribution of participants according to their answers (in percentages) and mean satisfaction score

Item	Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Mean score		
						FM	GP	Both
My doctor has a good understanding of my problem	2.3	5.0	5.0	66.3	21.4	4.09	3.91	4.00
My doctor tells me about medicines prescribed in a language that I understand	0.8	4.7	2.3	68.2	25.0	4.28	3.93	4.10
My doctor always takes me seriously	1.8	4.2	8.8	64.2	21.0	4.08	3.90	3.99
My doctor answers all my questions and concerns	2.0	7.0	1.8	63.8	25.4	4.20	3.88	4.04
My doctor doesn't listen to me with attention and patience*	29.7	46.0	4.0	16.0	4.3	3.73	3.89	3.81
My doctor examined me properly as I expect	2.8	9.5	6.7	58.3	22.7	3.98	3.80	3.89
My doctor showed good knowledge in his field	1.0	5.0	19.7	52.3	22.0	3.99	3.80	3.89
My doctor gave me appropriate follow up appointment	1.8	12.5	25.5	43.2	17.0	3.80	3.43	3.61
My doctor gave me privacy during my visit	1.8	6.5	4.5	63.0	24.2	4.13	3.91	4.01
My doctor looks neat with professional outlook	0.8	2.8	5.7	65.7	25.0	4.28	3.96	4.12
My doctor did his best to keep me from worrying about my problem	1.8	5.3	8.5	60.2	24.2	4.14	3.86	4.00
My doctor was interested in all my health problems	1.8	9.3	7.4	59.3	22.2	4.04	3.79	3.91
Some of the examination procedures my doctor used were unnecessary*	20.2	46.0	27.0	6.0	0.8	3.94	3.65	3.79
My doctor treated me with respect and concern	1.3	1.0	1.3	59.7	36.7	4.43	4.16	4.30
I think my doctor office has everything needed to provide good medical care	5.5	8.5	15.3	53.5	17.2	3.54	3.84	3.69
My doctor made me feel foolish*	56.0	39.4	2.3	2.0	0.3	4.49	4.50	4.49
My doctor did not give me suggestions on what I could do to help my problem*	28.0	51.5	5.5	12.5	2.5	3.94	3.87	3.90
My doctor gave me advice on how to prevent health problems from occurring.	4.0	13.3	6.0	57.7	19.0	3.84	3.65	3.75
I think my doctor should have spent more time with me*	10.5	48.7	12.3	25.0	3.5	3.37	3.39	3.38
Overall I am satisfied and I will recommend this doctor to others.	2.3	6.3	8.8	59.4	23.2	4.07	3.83	3.95
Overall mean score						4.02	3.85	3.93

*Scores were reversed (Strongly disagree 5, Disagree 4, Neutral 3, Agree 2, Strongly agree 1)
 FM = Family Medicine; GP = General Practitioners

visit (77%). The median number of visits last year was higher in FM than GP setting ($p = 0.03$).

Table 2 shows characteristics of the treating practitioner as reported by participants. There was no significant difference in practitioners' gender between FM and GP healthcare settings. However, Kuwaiti practitioners were more prevalent in

FM (60%) while non-Kuwaiti practitioners were predominant in GP setting (74%), a difference which was statistically significant ($p < 0.001$). Also, there was a significant difference between the two settings regarding age whereas older practitioners (≥ 50 years old) were more prevalent in GP (12%) than in FM setting (2%, $p = 0.001$).

Table 4: Comparison between patient satisfaction of FM and GP practitioners

Patient satisfaction	Primary Healthcare Practitioners				p-value
	FM (n = 200)		GP (n = 200)		
	n	(%)	n	(%)	
Dissatisfied (Satisfaction score < 60)	12	(6.0)	11	(5.5)	< 0.001 ^a
Satisfied (Satisfaction score 60 - 80)	100	(50.0)	154	(77.0)	
Highly satisfied (Satisfaction score > 80)	88	(44.0)	35	(17.5)	
Overall satisfaction score (out of 100) Mean ± SD	78.4 ± 10.7		75.2 ± 8.2		

FM = Family Medicine; GP = General Practitioners; a = chi-square test.

Satisfaction items and score:

Table 3 exhibits the percentages of participants who answered patient satisfaction items and the mean score for each item. Item mean scores ranged from 3.38 out of five in the item "I think my doctor should have spent more time with me" to 4.49 in the item "My doctor made me feel foolish" where 56% strongly disagreed, 39.4% disagreed and only 2.3% agreed. The satisfaction mean score was also low in the items "My doctor gave me appropriate follow-up appointment" (3.61), "I think my doctors office has everything needed to provide good medical care" (3.69) and "My doctor gave me advice on how to prevent health problems from occurring" (3.75). Of those satisfaction items which received high mean scores were "My doctor treated me with respect and concern" (4.30), "My doctor looks neat with professional outlook" (4.12), and "My doctor tells me about medicines prescribed in a language that I understand" (4.10). The overall satisfaction mean scores were 4.02 in FM, 3.85 in GP ($p = 0.001$) and 3.93 out of 5 in both settings.

Table 4 compares between patients satisfaction scores in FM and GP settings. The total satisfaction score ranged from 20 to 100 for the 20 satisfaction items. The level of satisfaction significantly varied between FM and GP settings ($p < 0.001$). In FM 44% of participants reported to be highly satisfied compared to 17.5% in GP practice. The mean total satisfaction score in FM (78.4 ± 10.7 out of 100) was higher than that of GP (75.2 ± 8.2 , $p = 0.047$).

Variation of satisfaction score according to socio-demographic characteristics and the type of treating practitioner:

Table 5 presents the variation of the mean patient satisfaction score according to socio-demographic characteristics of patients and treating practitioners in FM and GP settings. In GP, female patients reported higher satisfaction score (78.4 ± 8.3) than males (75.2 ± 9.7 , $p = 0.02$), whereas in FM no difference could be detected. In the family medicine setting, the extent of patient satisfaction

Table 5: Variation of the mean patient satisfaction score according to socio-demographic characteristics of patients and treating practitioners

Variable	FM			GP		
	Mean	SD	p-value	Mean	SD	p-value
Patient age (in years):						
< 30	80.4	10.2		76.4	9.9	
30 - 49	80.2	12.2	0.989	76.4	8.7	0.121
≥ 50	80.5	12.7		80.3	7.3	
Gender:						
Male	79.9	13.4	0.719	75.2	9.7	0.013
Female	80.5	10.6		78.4	8.3	
Marital status:						
Single	80.4	10.7		75.8	9.3	
Married	80.9	11.9	0.193	77.3	9.1	0.537
Divorced/Widowed	74.9	12.8		78.5	4.4	
Nationality						
Kuwaiti	81.1	11.8	0.060	76.9	9.1	0.905
Non-Kuwaiti	77.3	10.6		77.0	9.2	
Educational level						
Illiterate	81.0	7.9		78.2	7.2	
Elementary	79.4	9.7	0.329	77.8	7.3	0.121
Intermediate/Secondary	78.8	10.8		75.8	8.7	
University and above	81.9	12.7		77.9	11.0	
Occupation						
Unemployed	80.3	10.9		77.3	8.6	
Laborers	83.1	14.3		77.0	12.7	
Semi-skilled	82.4	12.7	0.280	76.4	8.2	0.309
Skilled	70.5	2.1		71.1	11.7	
Semi-professional	77.9	12.3		77.3	9.3	
Professional	70.0	6.5		79.4	3.7	
Family income:						
< 500	76.3	10.6		77.1	6.2	
500 -1000	79.6	10.8	0.020	76.4	9.0	0.832
> 1000	82.2	12.1		77.3	10.2	
Type of visit:						
First	79.8	9.8	0.747	74.3	10.1	0.019
Follow-up	80.4	12.1		77.7	8.6	
Practitioner						
Male	80.3	11.5	0.986	76.2	8.6	0.325
Female	80.3	11.8		77.5	9.6	
Practitioner's nationality						
Kuwaiti	80.7	11.5	0.540	78.6	11.5	0.191
Non-Kuwaiti	79.7	11.8		76.3	8.0	
Practitioner's age (in years)						
< 30	79.8	7.0		77.9	9.2	
30-50	80.3	4.8	0.877	76.4	9.2	0.377
> 50	83.0	9.3		79.0	8.3	

FM = Family Medicine; GP = General Practitioners

significantly increased as family income increased. The mean satisfaction score was 76.3, 79.6 and 82.2 for patients with family income < 500, 500 -1000 and > 1000 KD respectively ($p = 0.02$). In the GP practice, patients who were registered as follow-up visits were significantly more satisfied (mean

score = 77.7 ± 8.6) than those who were coming for the first visit (score 74.3 ± 10.1 , $p = 0.02$). The mean patient satisfaction score did not vary according to other socio-demographic characteristics of patients. Furthermore, patient satisfaction was not affected by gender, nationality or age of the treating practitioner in the FM nor GP settings.

DISCUSSION

The present study was based on the hypothesis that there is a difference in patient satisfaction level according to the type of healthcare practitioner in family medicine as compared to general primary care (GP) settings. Our data supports this hypothesis.

Socio-demographic characteristics:

The age and gender structure of the study group showed that half of the participants were 30 - 49 years old, with females being predominant in both settings. This may be attributed to the composition of the target population as more middle aged married women are expected to utilize the primary healthcare services for themselves as well as their offspring.

The present study showed that university educated, semi-professional patients of middle age and high family income were more prevalent in the FM settings. The rationale behind this may be that the FM primary healthcare services are highly preferred and widely utilized by such category of patients. Furthermore, the median number of follow-up visits was higher in the FM setting since an important role of FM practitioners is to provide continuous follow-up for whole families under their care to assist in monitoring their well-being.

Although there was no significant difference in practitioners gender between FM and GP healthcare settings, there was significant difference in practitioners' nationality among the two settings as well as in practitioner's age structure. Since only Kuwaiti nationals are accepted in the postgraduate FM program, a greater number of Kuwaiti FM practitioners were qualified to operate in the FM setting. As a consequence, more general primary healthcare centers were upgraded to become FM practices, starting with the Capital governorate. As a result, older middle aged non-Kuwaiti practitioners were relocated to the GP setting.

Satisfaction items and score:

In the present study, most participants were satisfied with the items related to "caring and respect" in the questionnaire, followed by "communication" items. The ability of practitioners to treat patients with respect and concern was acknowledged by most patients with mean

satisfaction score of 4.30 out of five. This result is consistent with another study, which concluded that about 36% of patient complaints were related to attitude, conduct or communication of practitioners with patients^[8]. Furthermore, in a study in Saudi Arabia, about two-thirds of patients reported that careful listening of the doctor to patient's complaints is an important characteristic of an ideal physician^[9]. Also, other studies have shown that practitioners communication skills (the length of time spent with patients, explaining and responding to their queries, offering reassurance and support, involving them in decision-making, discussing diagnostic test results and findings from physical examinations) were strong and important correlates of patients satisfaction^[1,10]. In addition, another study reported that patients were more satisfied when their physicians showed more of a customer approach in which they allowed patients to express themselves in their own words during the medical history, part of the interview, and when physicians were more informative in the treatment planning part^[11].

The least satisfied items were "I think my doctor should have spent more time with me" and "My doctor gave me appropriate follow-up appointment" This result is in concert with previous studies^[1,12,13] that the low mean patient satisfaction score in case of not giving follow-up appointment or offering request referral to hospitals was the result of physicians failing to perform according to patients expectations or to accommodate patients' demands. The levels of agreement between patient's expectations from healthcare providers and their perceptions about the actual performance of these providers have been shown to be associated with their level of satisfaction. Patient desires, particularly for follow-up appointments, may not be professionally justified and patients need to be educated about the objectives and limits of the primary healthcare services, and to be assured that all efforts will be undertaken to offer the most appropriate professional care at the primary or secondary healthcare level.

In our study, the item 'My doctor gave me advice on how to prevent health problems from occurring' received low satisfaction score. This is a very important finding since it indicates that there is a deficiency in the area of disease prevention, and that primary healthcare practitioners did not emphasize it. Indeed, one of the main goals of primary healthcare is disease prevention, and practitioners should assume an active role in that respect.

Our data showed that FM setting had higher patient satisfaction levels as compared to GP practice as denoted by a higher mean satisfaction score in

FM (78.4%) than in GP setting (75.2%). Also, in FM, 44% of patients were highly satisfied whereas the corresponding figure in GP was only 17.5%.

In similar studies conducted in other Gulf Countries such as United Arab Emirates and Qatar, the overall satisfaction scores were reported to be 81% and less than 60% respectively^[14,15]. In developed countries as USA, a satisfaction score of 75% was reported^[12]. This may be due the fact that FM physicians are professionally qualified as primary healthcare practitioners while GPs depend on their own experience and short time training course. Also, as mentioned before, an important role of FM practitioners is to provide continuous follow-up for whole families under their care to assist in monitoring their well-being. One of the reasons that the FM setting received higher patient satisfaction level than GP may be that most of the practitioners in FM setting are Kuwaiti nationals similar to patients in the Capital health region, and hence it may be easier for patients to build good relationships with practitioners of common cultural background. As patients had longer relationship with practitioners in the Family Medicine setting, they tended to perceive that the practitioner's warmth, professional care and communication were better^[13,16].

Variation of satisfaction score according to socio-demographic characteristics of patients and treating practitioner:

Many studies have reported variable association of satisfaction according to socio-demographic characteristics of patients. These studies discussed the association of patients socio-demographic characteristics with the overall satisfaction with services provided in primary healthcare setting rather than comparing patients satisfaction in FM setting to GP setting^[9,14,15,17]. The results of the present study indicated that female patients and patients with frequent follow-up visits were the most satisfied with GP practice. Our data also indicated that satisfaction level in FM practice was directly related to family income, *i.e.*, as family income increased the level of patients satisfaction increased. This may be attributed to the fact that family income is usually associated with a higher level of education and awareness. As a consequence, educated patients tend to be more aware of their rights and the limits of the primary healthcare role. However, other studies reported that females were less satisfied^[2,17] while another study concluded that age and gender of patients were of little importance in determining satisfaction with general practitioners in primary care practice^[19].

In addition, our study showed that patient satisfaction was not influenced by gender, nationality or age of the treating practitioner in either type of

primary healthcare setting which indicated that it is the health system itself that mainly affects patient satisfaction more than physician characteristics.

This patient satisfaction study has provided important information on several aspects of health services, including the quality of healthcare. A study of this nature is expected to help healthcare providers better understand patients' views which can be optimally utilized in planning, controlling and delivering healthcare services. This would eventually improve the healthcare system towards better patient welfare.

CONCLUSIONS

Overall, patient satisfaction score with primary health care practitioners in the capital health region was high. The study supported the hypothesis that patient satisfaction score with FM practitioners was higher than that of the GP due to several factors, an important one being better doctor-patient relationship in FM practice, as shown in the present study. Among the items that received high satisfaction scores were those related to doctor-patient relation: respect, concern, and better communication. However, follow-up appointments or hospital referrals that may not be professionally justified by primary healthcare professionals are perceived by patients as sources of dissatisfaction. Patient's gender, family income, and frequency of visits were significantly associated with satisfaction level. However, patient satisfaction level was not affected by gender, age, or nationality of the treating practitioner in either FM or GP settings.

There is a need to remedy the areas that received low level of patient satisfaction in the present study such as time spent with patients and follow-up appointments. Practitioners in primary health care should be trained and be ready to undertake an active role in disease prevention, since this was one of the areas which received low patient satisfaction in the present study.

Since the study showed low satisfaction with certain items considered as professionally unjustified, patients need to be educated about objectives and limits of the primary healthcare services since this can influence their level of satisfaction. Also, there is a need to continue conversion of GP to FM practice, since this study showed that patient's satisfaction was higher in family medicine than in the general practice setting.

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Original Article

GTN Ointment in the Treatment of Anal Fissures: Audit of Local Experience in Mubarak Al-Kabeer Hospital, Kuwait

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ABSTRACT

Objective: To evaluate the role of topical glyceryl trinitrate (GTN) ointment as a non-surgical treatment for anal fissure. Anal fissure is an ischemic disease caused by spasm of internal anal sphincter. Nitric oxide from GTN causes chemical sphincterotomy and improves blood flow, thus healing the anal fissure.

Design: Prospective study conducted from May 2003 to April 2004

Setting: Surgical outpatient clinic, Department of Surgery, Mubarak Al-Kabeer Hospital, Kuwait

Subjects: Eighty-six patients (42 male and 44 female) were recruited. Thirty seven patients had acute and 49 had chronic anal fissure.

Interventions: All patients were treated with topical 0.2% GTN ointment twice daily with additional application after defecation.

Main Outcome Measures: An independent observer

assessed the patients until full healing of fissures.

Results: Patient compliance was good. One patient developed transient mild headache. All patients achieved great reduction in pain score from a mean of 5.3 pre-treatment to 0.92 after one week and nearly zero at 4 - 6 weeks' treatment. Complete healing occurred at four weeks in all cases from the acute anal fissure group (100%) and in 37 patients (75.5%) from the chronic anal fissure group. Twelve (24.4%) unsuccessful patients with chronic anal fissure underwent surgical sphincterotomy. Recurrence occurred at two months in three patients (8.1%) with acute anal fissure requiring another course of GTN ointment, and in one patient (2.04%) with chronic anal fissure who required surgery.

Conclusion: GTN ointment for anal fissure should be considered as a first line treatment prior to surgical intervention in order to reduce complications of surgery.

KEYWORDS: anal fissure, first line treatment, GTN ointment

INTRODUCTION

Anal fissure is a common anal disease. Current theory suggests that the cause of healing failure is due to spasm of the internal sphincter which generates high pressure in the anal canal and leads to secondary local ischemia of the mucosa^[1-3].

Surgical lateral internal sphincterotomy is associated with troublesome incidence of minor form of anal incontinence (5.3 - 35.1%)^[4-7].

Nitric oxide (NO) has been shown to be an inhibitory neurotransmitter in the internal anal sphincter^[5,6,8]. Glyceryl trinitrate (GTN) ointment applied to the anus leads to a significant fall in maximum anal resting pressure (MARP) by 20-27% and an increase in anoderm blood flow, thus resulting in healing of the fissure^[3,9-11].

PATIENTS AND METHODS

Between May 2003 to April 2004, 86 patients with

anal fissure were prospectively studied. There were 42 male (48.8%) and 44 female (51.1%) subjects, with a mean age of 40 years (range 20 - 60 years). Acute anal fissure was seen in 37 (43.02%) and chronic anal fissure in 49 patients (56.9%). The site of anal fissures was posterior in 79 patients (92%), anterior in four women (4.6%) and both anterior and posterior in three women (3.4%)

All patients were treated with topical 0.2% GTN ointment twice daily with additional application after defecation. An independent observer assessed the patients and did the follow up was until full clinical healing of the anal fissure. Pain score (from 0-10), clinical examination, compliance and side affect of the treatment were recorded. Complete reduction of clinical symptoms and re-epithelialization of the lesion defined healing of the fissure. Patients with additional anorectal disease or prior anorectal surgery were excluded from this study.

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Table 1: Result of GTN treatment for acute and chronic anal fissure

	Acute Anal Fissure n (%)	Chronic Anal Fissure n (%)
Total number of patients	37	49
Healing at 6 weeks	37 (100)	37 (75.5)
Failure	-	12 (24.4)
Recurrence	3 (8.1)	1 (2.04)

RESULTS

A total of 86 patients were treated over the 12 months period with 0.2% topical GTN ointment. All were compliant with the topical GTN treatment as prescribed. There was great pain relief, as the mean pain score decreased from 5.3 in the pre-treatment period to 0.92 after one week of treatment and nearly to zero at 4 - 6 weeks treatment.

There was progressive epithelialization of the anal fissure with complete healing at four weeks in all cases of acute anal fissures and in 37 (75.5%) patients of chronic anal fissure. In the chronic anal fissure group, 12 patients (24.4%) failed to respond and underwent surgical lateral sphincterotomy.

Transient mild headache was reported by one patient (1.16%). However, this did not require discontinuing the treatment. None of our patients developed the potential side effect of GTN therapy such as hypotension, syncope, rebound hypertension, crescendo angina or allergic dermatitis.

At two months follow-up after full healing of the anal fissure there were three recurrences in the acute anal fissure group that were treated successfully with another course of GTN ointment. In the chronic anal fissure group there was one recurrence that required surgery (Table 1).

DISCUSSION

GTN belongs to the group of organic nitrates. Their action is derived from their metabolic conversion to nitric oxide in the vascular smooth muscle cells^[11]. It also plays an important role in nonadrenergic, noncholinergic nerve-mediated relaxation of gastrointestinal smooth muscle including the anal sphincter^[3,12]. Passive diffusion of GTN, a nitric oxide donor, through normal skin leads to therapeutic plasma level, mediating relaxation of the smooth muscle after a few minutes^[11].

Myenteric nerves innervating the internal sphincter muscle of the anus produce and release nitric oxide, mediating relaxation of this muscle^[13,14]. Derangement in the nitric oxide regulation may underlie the anal-sphincter hypertonicity associated with anal fissure and ulcer^[13].

From various studies, it was established that nitric oxide is the most important inhibitory neurotransmitter of the internal anal sphincter^[3,8,9,11,13,15,16]. GTN is one of the groups of organic nitrates that bind to protein receptors releasing nitric oxide. This leads to a fall in maximum anal resting pressure and increase in the anodermal blood flow. Interestingly, it was found that the patients who applied GTN reported a greater amelioration of pain than those using local anesthetic (lidocaine). This indicates the additional effect of GTN in improving vascular perfusion^[3,8,9,11,13,15,16].

Our results revealed great satisfaction of patients with the treatment, as it did not interfere with their life activities and avoided surgery. In addition, the healing rate with treatment was 75.5% with chronic anal fissure and 100% in acute anal fissure; this was associated with a low rate of side effects (1.16%, one patient). That patient developed a transient mild headache, which was self-limiting, did not interfere with the patient's daily activities and/or require discontinuation of GTN ointment treatment.

Nitroglycerin has been used as an antianginal agent since 1879; the adverse reactions were related to its activity as a vasodilator and were proportional to dosage^[17]. Although headache is the most common complication of nitrate therapy of coronary artery disease, other complications such as hypotension, syncope, rebound hypertension, crescendo angina or allergic dermatitis may occur. The relatively small dosages used in the treatment of anal fissures may be responsible for the low incidence of side effects^[18].

Resistant or insensitive internal anal sphincter to the endogenous nitric oxide, shorter duration of action of glyceryl trinitrate of less than eight hours and the development of tachyphylaxis (a previously effective dose becoming ineffective with time) are some of the possible reasons for failure GTN treatment for anal fissure^[19,20].

In our study, the use of GTN was associated with a great reduction in mean pain score from 5.3 to 0.92 after one week of treatment and nearly zero at four weeks. The failure rate was 12.94% in chronic anal fissure group. Those patients were treated with lateral sphincterotomy. Many studies have shown that GTN treatment failure for anal fissure was associated with failure of reduction of maximum anal resting pressure^[10].

CONCLUSION

Application of GTN ointment as a local treatment for anal fissure should be considered as first line treatment to reduce complications of surgery. However, it will not be able to obviate surgery in some patients with chronic anal fissure, but will still be able to reduce the rate of surgery in general.

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Original Article

Risk Factors for Coronary Heart Disease among Diabetic Patients

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ABSTRACT

Objective: To assess the prevalence of risk factors for coronary heart disease (CHD) and to calculate a 10-year CHD risk among diabetic patients in Kuwait.

Design: Cross-sectional study.

Setting: Fahaheel Specialty Clinic, Ahmadi Health District, Kuwait.

Subjects and Methods: Two hundred adult diabetic patients of either sex (type 2) were included in the study. Data was collected on patients' demographic background and different clinical investigations.

Main Outcome Measures: The calculated Framingham global risk estimate of a 10-year risk of CHD.

Results: The data showed a high prevalence of multiple

risk factors for CHD among diabetic patients. Among men 28% had low risk for CHD ($\leq 10\%$ 10-year risk), 29% had moderate risk for CHD (between a 10 and 20% 10 year risk), and 45% had high risk for CHD (greater than 20% 10 year risk). Forty percent of women had low risk, 33% had moderate risk and 27% had high risk for CHD.

Conclusions: Multiple risk factors for CHD are prevalent among the studied patients with type 2 diabetes. This illustrates the need for more in-depth research on this subject. It is also an imperative that primary health care for diabetic patients in Kuwait involves an increased awareness on how to mitigate such common risk factors for CHD.

KEY WORDS: coronary heart disease, diabetes, risk factors

INTRODUCTION

Coronary heart disease (CHD) is one of the leading causes of death. According to the World Health Organization, in 2002, there were 7.22 millions deaths from CHD globally^[1]. It predicts 11.1 million deaths from CHD in 2020^[2]. Diabetes mellitus (DM) is well-established as one of the strongest risk factors for CHD^[3]. Though an association between these two diseases was recognized as early as the late 1800s, CHD was an infrequent cause of death in diabetic patients in the pre-insulin era. Since 1922, mortality rates from infections, gangrene, and coma have fallen with consequent proportional rise in vascular diseases^[4].

Obesity is a strong risk factor for CHD^[5]. It has been shown to be a major health problem and it is associated with many conditions such as DM, CHD, gall bladder disease, hypertension, osteoarthritis and cancer^[6]. The majority of type 2 diabetic patients are overweight and the prevalence of diabetes is increasing in parallel with that of obesity^[7]. Both hypertension and diabetes are common conditions and the prevalence of hypertension is higher in

diabetic subjects than in those without diabetes^[8]. Both high cholesterol and high triglycerides levels are common in DM^[9,10].

Both type 1 diabetes and type 2 diabetes increased the risk for CHD^[11,12]. Type 2 diabetes is of a particular concern since it is so common and usually occurs in individuals of advancing age, when multiple other risk factors co-exist^[13]. An estimated 150 million people have type 2 diabetes globally. This figure is expected to double by 2025^[14].

A study has shown that cigarette smoking is a risk factor for hypertension and smokers have a five fold increased risk of hypertensive crisis^[15]. Cigarette smoking also has been shown to affect lipid levels by lowering HDL cholesterol and raising LDL and triglycerides levels. In addition, nicotine stimulates the release of epinephrine, which can make hypertension more difficult to control^[16].

Researchers found that the prevalence rate of DM in Kuwait was 15% in 1997^[2]. It was found in 41% of the total hospital patients in Kuwait^[17]. A recent study has shown an increased prevalence of obesity^[18] and it was found to be the most common

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Appendix 1: CHD risk prediction sheet for women

Step 1			Step 4		Step 7	
Age (Years)	Points		Diabetes	Points	(determine CHD risk from point total)	
30-34	-9		No	0	Point Total	10 year CHD Risk
35-39	-4		Yes	4		
40-44	0		Step 5 Smoker	Points		
45-49	3					
50-54	6					
55-59	7					
60-64	8					
65-69	8					
70-74	8					
Step 2					Step 6 (sum steps 1-5)	
Total Cholesterol			Adding up the points		-1	2%
(mg/dl)	(mmol/l)	Points	Age	----	0	2%
< 160	≤ 4.14	-2	Total Cholesterol	----	1	2%
160-199	4.15-5.17	0	Blood Pressure	----	2	3%
200-239	5.18-6.21	1	Diabetes	----	3	3%
240-279	6.22-7.24	1	Smoker	----	4	4%
≥ 280	≥ 7.25	3	Point Total	----	5	4%
Step 3					6	5%
Blood Pressure					7	6%
Systolic (mmHg)			Diastolic		8	7%
					9	8%
< 120	-3 pts				10	10%
120-129		0 pts			11	11%
130-139			2 pts		12	13%
140-159				3 pts	13	15%
≥ 160				0 pts	14	18%
					15	20%
					16	24%
					≥17	≥27%

risk factor among diabetic patients in Kuwait^[19]. A previous study showed that obesity and physical inactivity were documented in diabetic Kuwaiti adults^[20].

Various studies have been carried out in the United States, notably the Framingham heart study in Massachusetts to provide a simple way of classifying the overall risk level for CHD using a set of risk factors^[21,22]. The objectives of this cross-sectional study were to assess the prevalence of risk factors for CHD and to calculate a 10-year CHD risk among diabetic patients in Fahaheel area in Kuwait.

PATIENTS AND METHODS

Fahaheel Speciality Clinic provides health care to a total population of 63,487 in Kuwait. One of its services is to deliver health care to 16,000 registered diabetic patients in four diabetic clinics^[23]. Using the Framingham heart study as a base, a convenient sample of 200 type 2 diabetic patients participated in this study to assess and determine their risk levels for CHD in the next 10 years. All patients were aged 30-74 years and they were taking medication for diabetes. The patients were asked to answer a questionnaire after taking their consent. The Ethical Committee in the Ministry of Health had approved the study.

The questionnaire was designed to include the patients' demographic data and social habits

Appendix 2: CHD risk prediction sheet for men

Step 1			Step 4		Step 7		
Age (Years)	Points		Diabetes	Points	(determine CHD risk from point total)		
30-34	-1		No	0	Point Total	10 year CHD Risk	
35-39	0		Yes	4			
40-44	1						
45-49	2						
50-54	3						
55-59	4		Step 5				
60-64	5		Smoker	Points			
65-69	6		No	0			
70-74	7		Yes	2	≤-1	2%	
Step 2			Step 6 (sum steps 1-5)		0	3%	
Total Cholesterol			Adding up the points		1	3%	
(mg/dl)	(mmol/l)	Points	Age		2	4%	
< 160	≤ 4.14	-3	Total cholesterol		3	5%	
160-199	4.15-5.17	0	Blood pressure		4	7%	
200-239	5.18-6.21	1	Diabetes		5	8%	
240-279	6.22-7.24	2	Smoker		6	10%	
≥ 280	≥ 7.25	3	Point Total		7	13%	
Step 3					8	16%	
Blood Pressure					9	20%	
Systolic (mmHg)	<80	80-84	85-89	90-99	≥100	10	25%
	< 120	0 pts				11	31%
	120-129	0 pts				12	37%
	130-139		1 pts			13	45%
	140-159			2 pts		≥14	≥53%
	≥ 160				3 pts		

such as cigarette smoking and physical activity. It also included the treatment and control of type 2 diabetes, the date of first diagnosis and the date of the last admission for complications. Family history of type 2 diabetes in first degree relatives, side effects of drugs taken and other illnesses was also recorded.

Results of a thorough medical examination and measurements of weight and height were all recorded and body mass index (BMI) was calculated as kg/m². A series of biochemical measurements of serum cholesterol, serum triglycerides, serum creatinine, serum protein, urea, uric acid, albumin/globulin ratio, blood urea nitrogen and urine examination were all performed. In addition, a resting 12 lead ECG, chest X-ray and examination of the optic fundi were carried out.

Regarding the clinical investigations, BMI equal or above 25 was considered overweight or obese^[24]. The fasting values of the blood cholesterol exceeding 5.2 mmol/l, were considered high. Triglycerides levels above 2 mmol/l were considered high. Chest X-ray results were considered normal when no left ventricular hypertrophy (LVH) was seen. Eye investigations were considered normal when no retinopathy, cataract, and glaucoma were found. ECG results were considered normal when no LVH, ischemia, right bundle branch block (RBBB), supraventricular tachycardia, cardiomegaly, and atrioventricular block (AV block) were observed.

Table 1: General characteristics of diabetic patients

Variables	Men (n = 69)		Women (n = 131)		Total (n = 200)		p-value
	n	%	n	%	n	%	
Age (years)							
30 - 55	58	84.1	88	67.2	146	73.0	0.031
56 - 60	8	11.6	26	19.8	34	17.0	
> 60	3	4.3	17	13.0	20	10.0	
Family history of CHD							
No	38	55.1	49	37.4	87	43.5	0.017
Yes	31	44.9	82	62.8	113	56.5	
Physical activities							
No	2	2.9	84	64.1	86	57.0	0.00
Yes	67	97.1	47	35.9	114	43.0	
Smoking							
No	36	52.8	127	96.9	163	81.5	0.00
Yes	33	47.8	4	3.1	37	18.5	

p < 0.05 is significant

Table 4: Framingham Global Risk Estimate

Global Risk Estimate	Men (n = 69)		Women (n = 131)		p-value
	n	%	n	%	
Low (≤ 10%)	19	28	52	40	0.061
Moderate (10 - 20%)	20	29	43	33	
High (> 20%)	30	43	36	27	

p < 0.05 is significant

Finally, blood pressure was classified as optimal (when systolic < 120 mmHg and diastolic < 80 mmHg), normal (when systolic 120-129 mmHg or diastolic 80-84 mmHg), high normal (when systolic 130-139 mmHg or diastolic 85-89 mmHg), hypertension stage I (when systolic 140-159 mmHg or diastolic 90-99 mmHg), and hypertension stage II-IV (when systolic ≥ 160 or diastolic ≥ 100 mmHg)^[25].

Absolute 10 year CHD risk was calculated using the CHD risk prediction score sheet and the Framingham global risk estimate of 10 year risk for men and women (Appendices 1 and 2). This estimate was used for each participant to determine the probability of having a heart attack or dying of CHD during a 10 year period^[3].

Data analysis was performed using the SPSS data analysis system with chi-square test to demonstrate the significance of different variables.

RESULTS

Table 1 shows the general characteristics of diabetic patients. Out of the 200 diabetic patients, the majority, 131 (65.5%) were women and the remaining, 69 (34.5%) were men. The vast majority of men and women (84.1% and 67.2% respectively) were between 30-55 years of age. Presence of family history of CHD in first degree relative was recorded in more than half (113, 56.5%) of the total patients. The physical activity level was decreased among most women (64.1%). Smoking was recorded in

Table 2: Clinical investigations of diabetic patients

Variables	Men (N = 69)		Women (N = 131)		Total (N = 200)		p-value
	n	%	n	%	n	%	
BMI							
Low	29	42.1	9	6.9	146	19.0	0.000
High	40	57.9	122	93.1	34	81.0	
Chol							
Low	34	49.0	41	32.0	87	37.5	0.016
High	35	51.0	88	68.0	113	62.5	
TGL							
Low	48	71.0	62	50.0	86	57.6	0.007
High	20	29.0	61	50.0	114	42.4	
Chest X-rays							
Normal	67	97.0	109	83.0	163	88.0	0.988
Abnormal	2	3.0	22	17.0	37	12.0	
ECG							
Normal	52	75.0	68	52.0	163	60.0	0.004
Abnormal	17	25.0	63	48.0	37	40.0	
Eye complications							
No	62	90.0	84	64.0	163	73.0	0.004
Yes	7	10.0	47	36.0	37	27.0	

p < 0.05 is significant, Chol = cholesterol, TGL = triglycerides, BMI = body mass index

Table 3: Distribution of the study subjects according to gender and blood pressure

	Blood Pressure				p-value
	Systolic (mm Hg)	Diastolic (mm Hg)	Men (n = 69) n %	Women (n = 131) n %	
Normal (incl. optimal)	< 130	< 85	15 22	6 5	0.00
High normal	130-139	85-89	18 26	24 18	
Hypertension stage I	140-159	90-99	30 43	66 50	
Hypertension stage II-IV	≥ 160	≥ 100	6 9	35 27	

p < 0.05 is significant

only 37 (18.5 %) patients. Half of men (36, 52.2%) were smokers and only four (3.1%) women were smokers. Significant differences existed between men and women in age, family history of CHD, physical activities, and smoking (p < 0.05).

The results of the various clinical investigations are shown in Table 2. The vast majority (93.1%) of women were either overweight or obese. More than half (57.9%) of men were either overweight or obese. Cholesterol levels were recorded high in 68% women and 51% of men. High triglycerides levels were recorded in half of women (50%) and 29% in men. Abnormal chest X-rays were found in 3 and 17% men and women respectively. Forty eight percent women and 25% men showed abnormal findings in the electrocardiogram (ECG). Thirty six percent women and only 10% men showed abnormal eye complications. Significant differences in all clinical investigations except chest X-ray were observed between men and women (p < 0.05).

The distribution of patients according to gender and blood pressure is shown in Table 3. Because there were relatively few subjects at the higher

stages of hypertension, stages II, III, and IV were combined into a single category. Approximately half of the subjects for both men and women had blood pressure levels in the hypertension stage I category. Blood pressure was 22% for normal (including optimal), 26% for high normal, and 9% for stage II-IV hypertension among men. The corresponding values were 5% for normal (including optimal), 18% for high normal, and 27% for stage II-IV hypertension among women. A significant difference in blood pressure was observed between men and women ($p < 0.05$).

The Framingham global risk estimation for both men and women is shown in Table 4. Among the 69 men who participated, 19 (28%) had low risk, 20 (29%) had moderate risk and 30 (43%) had high risk for CHD. Fifty two women (40%) had low risk, 43 (33%) had moderate risk and 36 (27%) had high risk for CHD. However, no significant difference in global risk estimate existed between men and women ($p > 0.05$).

DISCUSSION

The objectives of this study were to assess the prevalence of risk factors for CHD and to calculate a 10-year CHD risk among diabetic patients in Fahaheel area in Kuwait. To our knowledge, our study is the first that used the Framingham heart study to calculate a 10-year CHD risk levels among diabetic patients in Kuwait. The results of this study suggested a high prevalence of multiple risk factors for CHD among diabetic patients namely obesity, physical inactivity, smoking, family history, and elevated levels of cholesterol and triglycerides. Previous literature also showed similar findings^[26].

Our study showed that the prevalence of obesity was high among these diabetic patients. This is consistent with several studies that reported the prevalence of obesity in Kuwait to be higher than reported figures in the world^[27]. Our study also showed that most women reported a decreased level of physical activity. This is supported by previous studies that showed obesity to be high in Kuwait, especially in women and it could be a reflection of the sedentary life style and modernization^[20, 26, 28].

Smoking was prevalent among half (52.2%) the men and only in 3.1% women. This finding is consistent with a similar study done in Kuwait that showed 0.5% of women to be smokers^[29]. Approximately half of the subjects for both men and women had blood pressure levels in the hypertension stage I category. This finding is consistent with similar study done in Kuwait which showed that hypertension was seen in approximately half of the diabetic men and women^[19].

We also found that in men risks of having a heart attack or dying of heart disease in the next

10-years were 28% (low), 29% (moderate), and 43% (high) respectively. Regarding women, risks of having a heart attack or dying of heart disease in the next 10 years was 40% (low), 33% (moderate) and finally 27% (high) respectively. Although this risk estimation for both men and women was calculated using CHD prediction score and the Framingham risk estimation it does not include all risk factors for CHD which may contribute greater risk than revealed from summation of the major risk factors^[22].

We believe that the primary health care physicians, nurses, and other health professionals play a vital role in reducing the risk of CHD. This could be achieved primarily by communicating these risks to patients. This, in turn may motivate them to improve awareness and management of CHD risk factors. Consequently, this would help in reducing their weight, lowering their cholesterol level, controlling their blood pressure, and encouraging them to quit smoking.

CONCLUSIONS

Our results suggest that the multiple risk factors for CHD are prevalent among patients with type 2 diabetes in Fahaheel area in Kuwait. These factors were obesity, family history of CHD, physical inactivity, high cholesterol and triglycerides levels. Our results from the Fahaheel Clinic should not be generalized for all of Kuwait. We suggest that further studies with large samples are needed to explore the prevalence of risk factors for CHD among diabetic patients in other public and private speciality clinics in Kuwait.

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Original Article

Our Experience with Posturography in Hemiparetic Patients after Stroke in Kuwait

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ABSTRACT

Objectives: To study the Berg Balance Scale (BBS) as balance functional impairment of hemiparetic stroke patients after onset of stroke; to quantitatively assess control of balance by computerized dynamic posturography (CDP); to correlate composite equilibrium score (ES) with sex, side of lesion and stroke type; and to correlate ES with static and dynamic posturography in hemiparetic stroke patients.

Design: A retrospective case control study.

Setting: Outpatient clinic in Physical Medicine and Rehabilitation Hospital, Kuwait.

Subjects: A total of 21 hemiplegic ambulatory stroke patients and 19 age-matched healthy individuals as control group.

Interventions: BBS and CDP

Main Outcome Measures: ES and sensory organization test (SOT) 1-6.

Results : BBS scores of stroke patients were below the lower limit of the normal control group ($p < 0.001$).

Significant reduction was observed for composite ES of stroke patients compared to control group. Although no significant difference of static balance function was observed between patients and controls, significant reduction of dynamic balance function (SOT 4, SOT 5, SOT 6) was observed in stroke patients, compared to control group ($p < 0.05$).

In linear regression correlation (r) of stroke patients, no significant correlation was observed of ES with static balance function (SOT 1, SOT 2, SOT 3) in hemiparetic stroke patients ($p > 0.05$). However, there was a direct significant correlation of ES with dynamic balance function including SOT 4, SOT 5 and SOT 6 ($r = -0.71$; $p < 0.01$), ($r = 0.761$, $p < 0.01$) and ($r = -0.761$, $p < 0.05$) respectively in hemiparetic stroke patients.

Conclusions: Impaired dynamic equilibrium in stroke patients is likely to reflect reduction of muscle strength of the paretic side along with the possible impairment of sensory organization.

KEY WORDS: cerebrovascular accident, computerized dynamic posturography (CDP), postural instability (PI)

INTRODUCTION

Stroke has been identified as the most prevalent diagnosis among adults who fall^[1]. One third to one half of all people over the age of 65 years fall at least once per year^[2,3]. Balance is diminished in patients with hemiplegia and hemiparesis^[4,3]. Postural sway for patients with hemiplegia can be twice that of their age-matched peers^[5,6]. Symmetry of weight bearing is also impaired following stroke, with patients bearing as much as 61 to 80% of their body weight through their non-paretic lower extremity^[7,8]. Postural instability (PI), or impaired balance, is common in patients with stroke, especially as the disease severity advances^[8].

The term 'balance' refers to a multisystem function that strives to keep the body upright while sitting or standing and while changing posture. Balance is needed to keep the body oriented appropriately while performing voluntary activity, during external perturbations and when the support surface or

environment changes^[9]. Horak *et al.* proposed that balance (postural stability) requires three distinct processes: (i) sensory organization, in which one or more of the orientational senses (somatosensory, visual and vestibular) are involved and integrated within the CNS; (ii) a motor adjustment process involved with executing coordinated and properly scaled neuromuscular responses; and (iii) the background tone of the muscles, through which changes in balance are effected^[10].

Dynamic posturography has become an important tool for understanding standing balance in clinical settings. A key test in the NeuroCom International (Clackamas, Oregon) dynamic posturography system, the Sensory Organization Test (SOT), provides information about the integration of multiple components of balance. The SOT test leads to an outcome measure called the "Equilibrium Score" (ES), which reflects the overall coordination of the visual, proprioceptive,

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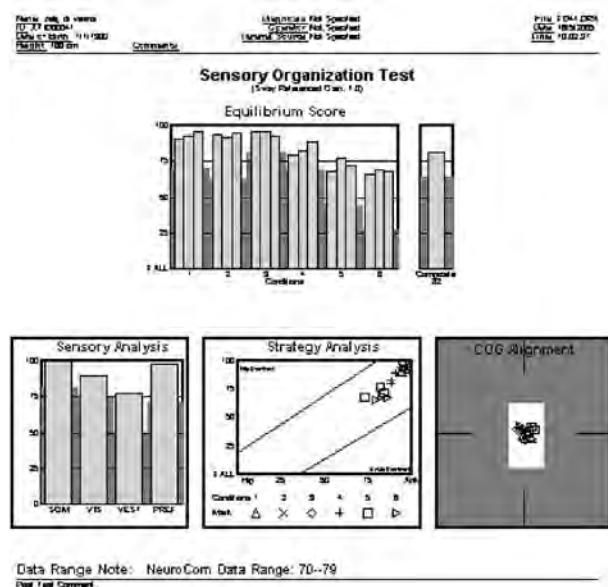


Fig. 1: Represents normal posturography with SOT, ES, static posturography (SOT 1, SOT 2 and SOT 3), dynamic posturography (SOT 4, SOT 5 and SOT 6)

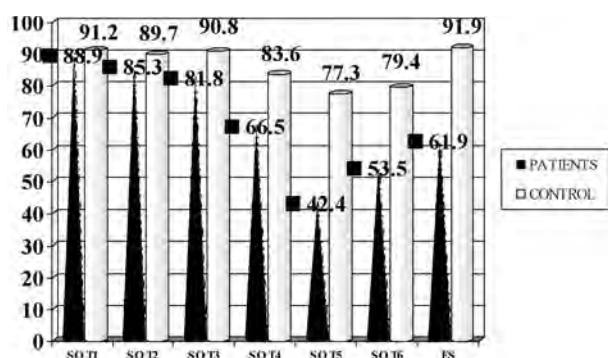


Fig. 3: Represents Mean (± SD) changes in The Composite ES and six tests conditions of SOT of hemiparetic stroke patients

and vestibular systems for maintaining standing posture. Researchers, therapists, and physicians often use the ES from the SOT as a clinically relevant measure of standing balance^[11].

PATIENTS AND METHODS

Subjects

A total of 21 hemiplegic but ambulatory stroke patients and 19 age-matched healthy individuals as control group admitted to the Balance Neurocom Clinic, Physical Medicine and Rehabilitation Hospital, Kuwait were recruited for this study. All patients and healthy individuals were evaluated clinically with a brief neurological examination (Table 1). All patients underwent image studies such as brain computed tomography (CT) or magnetic resonance imaging (MRI) to identify their stroke diagnosis during the acute stage.

Inclusion criteria for the trial were the following: (1) stroke within 30 to 150 days; (2) ability to ambulate 25 ft independently; and (3) mild to

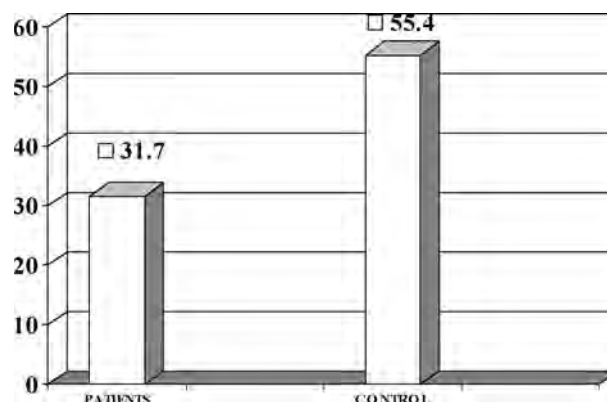


Fig. 2: Represents Mean (± SD) changes in BBS of hemiparetic stroke patients and control group

moderate stroke deficits defined by BBS (BBS) of 0 to 56 for upper and lower extremities.

Those with recurrent strokes, bilateral hemispheric, cerebellar or brain stem lesions, severe spasticity or cognitive deficit, orthopedic or peripheral neuropathy, significant visual field or hemineglect problems were excluded. Exclusion criteria also included (1) serious cardiac conditions (hospitalization for heart disease within three months, active angina, serious cardiac arrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, pulmonary embolus, or infarction), (2) oxygen dependence, (3) severe weight-bearing pain, and (4) other serious organ system disease. After subjects passed the screening criteria, an informed consent was taken for participation in this study.

Methods

All patients and healthy individuals were evaluated in a study of postural stability and balance using the BBS^[12] and computerized dynamic posturography (CDP)^[13].

Computerized dynamic posturography^[13]

All patients and healthy individuals were evaluated in a study of postural stability and sway in altered sensory conditions using CDP. The SMART Balance Master (NeuroCom International, Inc., Clackamas, OR, USA) was used for both balance function and assessment.

The SOT was performed in a clinically routine manner. The SOT included six tests conditions. The first three involved the patient standing on a fixed platform with eyes open (SOT 1), eyes closed (SOT 2), and using sway-referenced vision (SOT 3). The SOT of the patient standing on a fixed platform is called static posturography. The other three conditions ((SOT 4, SOT 5 and SOT 6) involved the patient standing on a moving platform including conditions 4 (eyes open), 5 (eyes closed), and 6 (using sway-referenced vision) and is called dynamic posturography^[13].

Table 1: Baseline demographic & clinical characteristics of hemiparetic stroke patients and control group

Characteristic	Stroke patients n = 21	Control group n = 19
Demographic Characteristics :		
Mean \pm SD Age in years	59.17 \pm 1.80	61.31 \pm 3.09
Gender- women / men	19 / 2	10 / 9
Clinical characteristics:		
Glasgow coma scale (0-15)	15 (15 - 15)	15 (15 - 15)
Mean \pm SE duration of stroke, wk	12.38 \pm 2.06 weeks	-
Hemianopia (0/1)	-	-
Fifth cranial nerve palsy	3 (14.3%)	-
Side of involvement	Left hemisphere 13 (61.9%) Right hemisphere 8 (38.1%)	-
Hemihypoesthesia	Left hemisphere 3 (14.3%) Right hemisphere 5 (23.8%)	-
Urinary incontinence (0/1)	-	-
High blood pressure	8 (38.1%)	-
History of heart attack	-	-
Diabetes	-	-
CT scan or MRI :		
Type of stroke n (%)	ischemic 16 (76.2) hemorrhagic 5 (23.8)	-

Table 3: Numerical Mean \pm SD of BBS in hemiparetic stroke patients and control group

Mean \pm SD	stroke patients	control group	Statistical analysis T- test (p-value)
Berge balance scale	31.7 \pm 1.8	55.4 \pm 0.7	Significant (p < 0.001)

Fig. 1 represents normal posturography with SOT including ES, static posturography (SOT 1, SOT 2 and SOT 3) and dynamic posturography (SOT 4, SOT 5 and SOT 6).

Statistical analysis

Study data were analyzed using the SPSS statistical package. The Student's *t* test indicates the magnitudes of the difference of means and therefore the magnitude of the observation. Thus, the unpaired *t* test was used to assess the difference between SOT scores of stroke patients and those of normal subjects. Prior to data analysis, the level of significance was established at $p < 0.05$. Linear regression correlation (*r*-) was also used to assess the relationship between ES and six tests conditions of SOT scores of stroke patients. A *p* value of ≤ 0.05 was used as level of significance.

RESULTS

The demographic and clinical characteristics of

Table 2: Mean \pm SE ES according to gender, side of involvement and type of stroke

Mean ± SE	Mean ES n = 21	Statistical analysis T- test (p value)
Gender		
Male	65,7143 ± 3.2	NS (p > 0.05)
Female	65,7143 ± 6.2	
Side of involvement		
Left hemisphere	61,2000 ± 5.1	NS (p > 0.05)
Right hemisphere	63,8333 ± 2.1	
Type of stroke		
Ischemic	61,4706 ± 3.6	NS (p > 0.05)
Hemorrhagic	64,0000 ± 7.2	
NS = not significant		

Table 4: Numerical Mean \pm SD of SOT including six tests conditions in hemiparetic stroke patients and control group

Mean \pm SD	stroke patients	control group	Statistical analysis T- test (p-value)
Composite ES (ES)	61.9 \pm 10.6	91.9 \pm 3.2	Significant (p < 0.05)
Static posturography (standing on a fixed platform)			
SOT 1 score	88.9 \pm 5.4	91.2 \pm 1.9	NS (p > 0.01)
SOT 2 score	85.3 \pm 4.2	89.7 \pm 3.2	NS (p > 0.05)
SOT 3 score	81.8 \pm 4.5	90.8 \pm 1.8	NS (p > 0.05)
Dynamic posturography (standing with the platform moving)			
SOT 4 score	66.5 \pm 7.9	83.6 \pm 5.3	S (p < 0.05)
SOT 5 score	42.4 \pm 11.8	77.3 \pm 4.6	S (p < 0.01)
SOT 6 score	53.5 \pm 15.6	79.4 \pm 3.0	S (p < 0.05)

NS = not significant, S = significant

all subjects are listed in Table 1. Table 2 represents correlation of mean \pm SE ES with gender, side of involvement and type of stroke in hemiparetic stroke patients. There were no significant differences of mean \pm SE of ES with gender, side of involvement and type of stroke in hemiparetic patients.

Table 3 and Fig. 2 represent numerical mean \pm SD score of BBS between patients and controls. BBS of stroke averaged below the lower limit of normal control group (p < 0.001).

Table 4 and Fig. 3 represent numerical mean \pm SD score of composite ES and six tests conditions of SOT between patients and controls. Significant reduction was observed for composite ES of stroke patients as compared with control group (p < 0.05). No significant difference was observed for the first

Table 5: Linear regression (r-) correlation of Mean \pm SD of the composite ES with six tests conditions of SOT in hemiparetic stroke patients

Mean \pm SD	Linear Regression (r-) of the Composite ES
Static posturography (standing on a fixed platform)	
SOT 1	No correlation ($r = 0.171$; $p > 0.051$)
SOT 2	No correlation ($r = 0.201$; $p > 0.051$) 0,201
SOT 3	No correlation ($r = 0.056$; $p > 0.051$).
Dynamic posturography (standing with the platform moving)	
SOT 4	direct significant correlation ($r = -0.710$; $p < 0.01$).
SOT 5	direct significant correlation ($r = 0.761$, $p < 0.01$)
SOT 6	direct significant correlation ($r = -0.667$, $p < 0.05$)

three conditions involving SOT 1, SOT 2 and SOT 3 between stroke patients and control group in static balance function (static posturography, $p > 0.05$). However, in dynamic balance function (dynamic posturography), significant reduction was observed for the other three conditions (SOT 4, SOT 5, SOT 6) of stroke patients as compared with control group ($p < 0.05$).

Table 5 represent linear regression correlation (r-) of ES with six tests conditions of SOT scores of hemiparetic stroke patients. No significant correlation was observed of ES with the first three conditions of static posturography (SOT 1, SOT 2 and SOT 3) in hemiparetic stroke patients ($p > 0.05$). However, in dynamic posturography there was a direct significant correlation of ES with SOT 4, SOT 5 and SOT 6 ($r = -0.71$; $p < 0.01$), ($r = -0.761$, $p < 0.01$) and ($r = -0.667$, $p < 0.05$) respectively in hemiparetic stroke patients.

DISCUSSION

CDP has become an important tool for understanding standing balance in clinical settings. A key test in the NeuroCom International (Clackamas, Oregon) dynamic posturography system, the SOT, provides information about the integration of multiple components of balance. The SOT test leads to an outcome measure called the ES, which reflects the overall coordination of the visual, proprioceptive, and vestibular systems for maintaining standing posture^[11].

In the sensory organization part of CDP, we have found that, the patient group showed significantly lower equilibrium performance as compared to the control group. In this study we have also found the differences between static and dynamic posturography. In static posturography,

mean scores of SOT 1, SOT 2 and SOT 3 with fixed platform were not significantly different between patients with stroke and controls. By contrast, on dynamic posturography (SOT 4, SOT 5, SOT 6), stroke patients showed significantly lower values of SOT 4, SOT 5&, SOT 6 for patients with stroke as compared to controls.

Thus, the majority of stroke patients could maintain static postural stability. But, dynamic postural control was impaired in stroke patients as risk factor for falls in people with stroke. The results suggest that patients with hemiparesis tend to fall easily and that the risk of falls toward the paretic side is high in moving in platform sway referencing on dynamic posturography (SOT 4, SOT 5 and SOT 6).

This study agrees with other studies of posture instability in patients with stroke by Ikai, Tetsuo *et al*^[14], de Haart M *et al*^[15] and Niam S *et al*^[16]. The dynamic postural control was impaired in patients with hemiparesis as compared with healthy subjects. The results suggest that patients with hemiparesis tend to fall easily and that the risk of falls toward the paretic side is high. The response latency to perturbations was longer and the response strength was weaker on the paretic side of patients with hemiparesis^[14,15].

Similar to previous investigations this study shows abnormalities of static posturography in stroke compared with healthy controls. However, dynamic balance was significantly impaired in patients with stroke whereas patients with stroke performed similarly to age matched healthy controls^[15] during static posturography. Significant differences in postural sway were found among different stances in eyes-open ($p = 0.00$ to 0.02) and eyes-closed conditions ($p = 0.00$ to 0.04) after stroke^[16]. Postural stability in quiet stance, was related to functional measures of balance as well as physiologic factors relating to balance, such as visual conditions, lower-extremity peripheral sensibility, motor recovery, and simple reaction time^[17].

The balance function of stroke patients was significantly worse as compared to that of the healthy subjects especially in dynamic stability. However, different from the other reports, our right hemispheric stroke patients had better balance function than left hemispheric patients. This result suggests that the motor function of the healthy limbs of stroke patients may play an important role in their balance function^[18].

The maintenance of balance when standing is a complex process that involves multiple peripheral sensory inputs, central integrating pathways, and efferent outputs. Postural sway presumably reflects noise and regulatory activity within this afferent-efferent control loops and seems to increase

in a non-specific fashion with impaired vestibular, somatosensory, or visual input.

Some authors reported that impaired dynamic equilibrium in stroke is likely to reflect a disruption of sensory, visual and vestibular input due to repetitive, involuntary head oscillations or motor weakness. Moving in platform sway referencing (SOT 4, 5 and 6) introduced changes in somatosensory input^[15].

Also, postural sway was related to visual condition, stance position, and proprioception^[16]. The response latency to perturbations was longer and the response strength was weaker on the paretic side of patients with hemiparesis. The dynamic postural control was impaired in patients with hemiparesis as compared with healthy subjects. The results suggest that patients with hemiparesis tend to fall easily and that the risk of falls toward the paretic side is high^[14].

In conditions of altered somatosensory information, with visual deprivation (ES 5) or visuovestibular conflict (ES 6), the median scores for patients with hemiplegia (ES 5 - 43; ES 6 - 20) were significantly lower than those for normal subjects (ES 5 - 69; ES 6 - 67). Many patients with hemiplegia seem to rely on visual input. Rehabilitation programs of postural control for the patients with hemiplegia should take into account the possible impairment of sensory organization and should include exercises to be performed under conditions of sensory input deprivation and sensory conflict^[19].

The stroke patients showed excessive postural sway and instability, particularly in the frontal plane, compared with reference values. It may be caused by weight-bearing asymmetry with disturbed sensibility or ankle^[15]. Postural sway was increased with more challenging standing conditions (*i.e.*, when multiple sensory systems were manipulated) to a greater extent with the stroke group as compared to controls. Muscle strength was only correlated to sway during the most challenging conditions. Furthermore, a greater number of persons with stroke fell during the balance testing compared to controls. Impairments in re-weighting / integrating afferent information, in addition to muscle weakness, appear to contribute to postural instability and falls in persons with stroke. These findings can be used by clinicians to design effective interventions for improving postural control following stroke^[20].

CONCLUSIONS

This study represents the first attempt to use of the CDP equipment as a diagnostic tool in assessment of the dynamic equilibrium performance in post-stroke patients in Kuwait.

Significant reduction was observed for composite ES of stroke patients as compared with control group. No significant difference was observed

in static balance function (static posturography). However, in dynamic balance function (dynamic posturography), significant reduction was observed in stroke patients as compared with control group ($p < 0.05$). Also, there was a direct significant correlation of ES with dynamic balance function (dynamic posturography) in hemiparetic stroke patients. Thus, our results suggest that impaired dynamic equilibrium was observed in stroke patients. This is likely to reflect reduction of muscle strength in the spine, hip and ankle of paretics along with the possible impairment of sensory organization which may be the main cause of their postural instability.

Further research in the use of this posturography equipment is needed to study the effects of visual feedback rhythmic weight-shift training on dynamic balance function in hemiplegic stroke patients.

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Original Article

Effects of the Fast of Ramadan on Endothelial Function and High-Sensitivity C - Reactive Protein in Newly Diagnosed Type 2 Diabetic Patients

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ABSTRACT

Objective: To evaluate the effect of fasting during Ramadan on the endothelial function and high-sensitivity C-reactive protein as a marker of inflammation in newly diagnosed type 2 diabetic patients.

Design: Prospective study.

Setting: Tertiary Center, Kuwait

Subjects: Fifty-two patients (29 male and 23 female) with newly diagnosed type 2 diabetes were examined, before and after the Ramadan fasting.

Intervention: A high resolution ultrasound scanner

Main Outcome measures: Assessment of endothelial function was done by ultrasound assessment of flow-mediated dilatation of the brachial artery. Also, both high-

sensitivity C-reactive protein and waist circumference were measured.

Results: Fasting during Ramadan significantly improved the brachial artery flow-mediated dilatation (7.27 ± 3.4 Vs. 5.27 ± 2 , $p < 0.05$) as well as significantly reduced both high-sensitivity C-reactive protein (0.26 ± 0.07 Vs. 0.48 ± 0.13 , $p < 0.001$) and waist circumference in both male and female group (94.68 ± 11.01 Vs. 92 ± 10.07 & 89.76 ± 17.52 Vs. 87.18 ± 17.53 , respectively, $p < 0.0001$)

Conclusion: Fasting during Ramadan has a beneficial effect on the endothelial function and on the reduction of low-grade inflammation and waist circumference.

KEY WORDS: C-reactive protein, endothelial dysfunction, high-sensitivity, Ramadan fasting, waist circumference

INTRODUCTION

Arterial inflammation has emerged as central to the progression of atherothrombosis^[1]. Of the markers of inflammation, the high-sensitivity C-reactive protein "hs-CRP" is the most studied, with evidence that it may also play a direct pathogenic role in atherosclerotic lesion formation^[2-9]. CRP, at concentrations known to predict adverse cardiovascular outcomes, directly inhibits the production of nitric oxide (NO) and angiogenesis, which could impair the response to ischemia^[10]. Serum CRP measured by a highly sensitive assay (hs-CRP) has become an important marker of vascular inflammation and predictor of atherosclerosis^[2,11-14]. Recent data suggest that hs-CRP is as important a predictor of atherosclerosis as circulating LDLC^[15]. Thus inflammation may be potentially as important as cholesterol in contributing to atherosclerosis. High levels of hs-CRP in obesity also predict development of diabetes later^[16].

Endothelium plays a vital role in vascular homeostasis, vascular tone regulation, vascular

smooth muscle cell proliferation, trans-endothelial leukocytemigration and thrombosis and thrombolysis balance. In response to various mechanical and chemical stimuli, endothelial cells synthesize and release a large number of vasoactive substances, growth modulators, and other factors that mediate these functions^[17]. Endothelial dysfunction is now regarded as an early pivotal event in atherogenesis and has been shown to precede the development of clinically detectable atherosclerotic plaques in the coronary arteries^[18]. This event was important in the development of microvascular complications in diabetes^[19].

Over the past decade, a non-invasive technique has evolved to evaluate flow-mediated vasodilatation (FMD) an endothelium-dependant function, in the brachial artery^[20-23]. This stimulus provokes the endothelium to release nitric oxide (NO) with subsequent vasodilatation (index of vasomotor function). This technique is attractive because it is non-invasive and allows repeated measurements.

Endothelial dysfunction in the brachial artery

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highly correlates with endothelial dysfunction in the coronary circulation, which is emerging as an independent risk factor for the cardiovascular disease^[24].

Diabetes is an atherosclerotic risk equivalent. Both are the end results of two important parallel pathways:

1. The progression of insulin resistance to the metabolic syndrome, pre-diabetes and ultimately diabetes and

2. The progression of endothelial dysfunction with progressive inflammation, thrombosis, and oxidation at the vessel wall to fatty streak formation and ultimately to the development of advanced atherosclerotic plaques^[25].

There has been much contention about the effect of Ramadan fasting on health. The majority of Muslims fast from dawn to sunset during the whole month of Ramadan. Ramadan is the ninth month in the lunar calendar. The daily fast (neither food nor drink) lasts about 12-19 hours depending on the season in which Ramadan falls and on the geographic location of the country.

The aim of our study was to evaluate the effect of Ramadan fasting on the link between endothelial function, inflammation and atherothrombosis.

PATIENTS AND METHODS

Study Population:

We recruited 52 patients with non-insulin dependant type 2 diabetes mellitus who were recently discovered (less than 3 years). None of our patients had documented coronary artery disease or history of myocardial infarction. A 12-lead resting ECG showed no ischemic ST-T wave changes and no pathological Q-wave. All patients had normal sinus rhythm. Also, none of our patients had cerebrovascular disorders, dysthyroid disease, heart failure, infection, vasculitis or peripheral vascular disease.

There were 29 male (age range 31-67 years, mean \pm SD 45 ± 17) and 23 female (age range 29 – 54 years, mean \pm SD 41 ± 15) patients. Seven out of 29 male patients were hypertensive (24.13%) and 18 were smokers (62.1%). Also, there were six hypertensives (26.1%) and seven current smokers (30.4%) in the female group.

Test samples were collected from all patients five and one week before Ramadan fasting and then one week after the beginning of Ramadan so that patients acted as their own control. Ethical Committee in the hospital approved the study.

All patients were educated about medications, hypoglycemia and hyperglycemia complications. They were asked to fill out a questionnaire about their meals, quantity, quality and they were advised to avoid the common practice of overfeeding with sweets. They were asked to adopt a protein-low fat-

energy restricted three meals before fasting (Iftar at sunset and Sohor before dawn). They were suitably monitored by a dietician.

Assessment of Flow Mediated Dilation in the Brachial Artery:

The ultrasound procedures for assessing endothelium function by FMD was performed as described in the guidelines by Corretti *et al*^[26]. The patients were examined in the morning after an overnight fast. None of our patients used long-acting nitroglycerine or calcium antagonist.

A high resolution ultrasound scanner (system Five GE Vingmed, Horton, Norway) with a 10.0 MHz linear array transducer was used. After a 10 minute equilibration period at rest in the recumbent position, scans of the brachial artery were taken proximal to the antecubital fossa and saved on videotapes. Baseline diameter recordings were obtained after which arterial occlusion was performed by inflating the forearm blood pressure cuff to 50mm Hg above systolic blood pressure for 4 - 5 minutes. After cuff release, diameter recordings were repeated during the post-occlusive increase in brachial artery blood flow.

Measurements of the brachial artery diameter was defined as the distance from the leading edge of the near wall intima-lumen echo to the leading edge of the far wall intima-lumen echo along a line perpendicular to the arterial long axis. A computer system with ultrasound tracing of echo interfaces was used for measurement of distance between the wall echoes within a 5 mm long section of the brachial artery. The brachial artery diameter was calculated in diastolic frames taken coincidentally with the R-wave on the ECG twice at rest and then 45, 60 and 75 seconds after cuff deflation. The average diameter at baseline and post inflation was calculated.

Guidelines expressed diameter changes as the percentage change relative to the mean baseline value. When baseline rest image was acquired, we estimated blood flow by time averaging the pulsed Doppler velocity signal obtained from a mid-artery sample volume. To assess the hyperemic velocity, we obtained the mid-artery pulsed Doppler signal upon immediate cuff release and no later than 15 s after cuff deflation.

Assessment of the Waist Circumference:

We measured the waist circumference at the narrowest point (between the highest point of iliac crest and the lower costal margin)^[27]. The normal values of waist circumference differ in both male and female population. Normal values for waist circumference in the male population should be

Table 1: Comparison of Pre and Post-fasting study parameters in the study group (n = 52).

Parameters	5-Weeks Pre-Fasting	1-Week Pre-Fasting	1-Week Post-Fasting
Baseline brachial artery diameter (mm)	3.52 ± 0.81	3.67 ± 0.79	3.59 ± 0.56*
Peak hyperemic blood flow (ml / min)	431 ± 135	434 ± 132	541 ± 95*
Blood flow increase (ml/min)	379 ± 82	365 ± 92	411 ± 87*
Flow-mediated dilatation (%)	5.25 ± 2.1	5.27 ± 2	7.27 ± 3.4*
High-sensitivity CRP (mg / dl)	0.47 ± 0.12	0.48 ± 0.13	0.26 ± 0.07*
Waist circumference in cm (Male group)	94.68 ± 11.01	95.1 ± 10.81	92 ± 10.07*
Waist circumference in cm (Female group)	89.67 ± 17.52	90.01 ± 17.34	87.18 ± 17.53*
Fasting blood glucose (mmol)	5.68 ± 0.38	5.63 ± 0.34	5.64 ± 0.38
Systolic blood pressure (mmHg)	123 ± 8	124 ± 9	122 ± 10
Diastolic blood pressure (mmHg)	80 ± 6	81 ± 4	79 ± 5

* = statistically significant

less than 102 cm, while that value in the female population should be less than 88 cm.

Assessment of hs – CRP:

High sensitivity C-reactive protein was processed with the use of latex- enhanced immuno nephelometric assays (Date Behring, Newark, Del.)^[28].

In patients without known cardiovascular disease, the range of hs-CRP for the subjects with the lowest (quintile 1) to the highest (quintile 5) vascular risk were 0.01 - 0.069, 0.07 - 0.11, 0.12 - 0.19, 0.2 - 0.38, and more than 0.38 mg/dl respectively. A risk estimate appears to be linear across the spectrum of inflammation and these sequential quintiles considered in clinical terms represent individuals with lowest, mild, moderate, high, and highest relative risks of future cardiovascular diseases.

Statistical Analysis

The statistical analysis was performed using SPSS^[11] software. Quantitative data were reported as mean ± standard deviation and compared using the students T-test. A linear regression analysis was used to study the relationship between the endothelial function and both the hs-CRP and waist circumference. A probability level of < 0.05 was considered statistically significant.

RESULTS

Effect of Ramadan Fasting on Endothelial Function

We studied 52 patients with recently diagnosed (less than 3 years, range 8-35 months) diabetes mellitus type 2 with no documented coronary artery, cerebro-vascular or peripheral vascular disease.

We examined patients twice before the Ramadan, by ultrasound to detect the endothelial dependant flow mediated vasodilatation in the brachial artery. The examination showed impaired flow mediated dilatation in the brachial artery both five weeks

and one week before the Ramadan (5.25 ± 2.1 Vs. 5.27 ± 2.0 p > 0.05). Ramadan fasting significantly improved flow mediated dilatation in the brachial artery diameter (7.27 ± 3.4 Vs. 5.27 ± 2.0 p < 0.05, post-fasting Vs. pre-fasting, percent change in brachial artery diameter, mean ± SD),

Pre-fasting blood sugar ranged between 5.1 - 6.5 mmol at five weeks and 5.0 - 6.2 mmol one week pre-fasting. Fasting blood glucose showed no significant difference after fasting (5.3 - 6.6 mmol, p > 0.05). Body weight was reduced post-fasting as compared to the week before fast (post-fasting 76.3 ± 5.6 Vs. pre-fasting 78.8 ± 4.98 kg).

Effect of Ramadan Fasting on hs-CRP:

The two test samples at five and one week prior to Ramadan were similar (0.47 ± 0.12 Vs. 0.48 ± 0.13, p > 0.05, mean ± SD). The third test sample (post Ramadan fasting) of hs – CRP showed significantly lower values than the second test sample (0.26 ± 0.07 Vs. 0.48 ± 0.13, mean ± SD, p < 0.001)

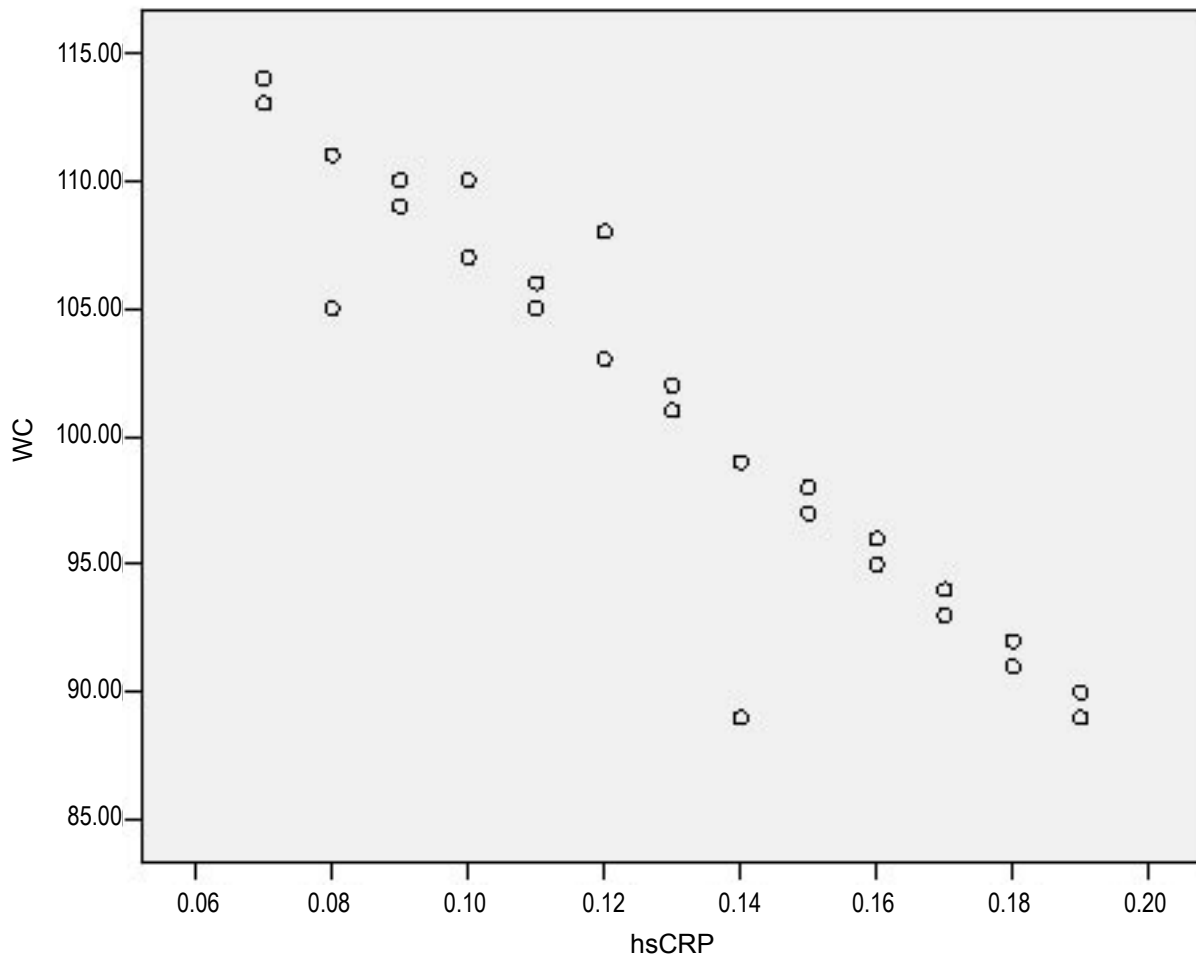
Effect of Ramadan Fasting on Waist Circumference:

In the male group, the waist circumference was significantly reduced after the Ramadan fasting (94.68 ± 11.01 Vs 92 ± 10.07, p < 0.0001, mean ± SD) with no significant difference between the waist circumference measurement at five weeks Vs. one week pre fasting (95.12 ± 10.9 Vs 94.68 ± 11.0, p > 0.05).

In the female group, the waist circumference was reduced significantly after the Ramadan fasting (89.76 ± 17.52 Vs 87.18 ± 17.53, p < 0.0001, mean ± SD) with no significant difference between the measurements of waist circumference at five weeks and one week before Ramadan (90.1 ± 16.9 Vs 89.76 ± 17.52, p > 0.05).

Relation between Endothelial Function, Hs- CRP and Waist Circumference:

There was an inverse relationship between



$r = 0.842; p < 0.0001$

Fig.1: Correlation between hs-CRP and waist circumference

the improvement in flow mediated dilatation in the brachial artery after Ramadan fasting and the reduction in the levels of hs - CRP ($r = -0.63, p < 0.0001$) as well as the reduction in the measurement of waist circumference ($r = -0.49, p < 0.001$).

DISCUSSION

We studied 52 patients with recently diagnosed type 2 diabetes (within the last three years) and no clinically evident macro-vascular disease (cardiovascular, cerebro-vascular or peripheral vascular disease). All our patients had impaired flow-mediated dilatation in the brachial artery (5.27 ± 2.0 baseline percent increase in brachial artery diameter, mean \pm SD)

A study by Williams *et al*^[29] as well as another study by Lim *et al*^[30] concluded that people with type 2 diabetes almost invariably have abnormal endothelial function as determined by the assessment of vascular reactivity and / or by the measurement of plasma markers of endothelial activation, coagulation, fibrinolysis, or inflammation. They have been consistently found

to have abnormal small and large vessel reactivity for both endothelium dependant and independent vasodilatory pathways, demonstrating that there is not only a reduction in nitric oxide production in diabetes but also decreased response to its effect in vascular smooth muscle cells.

In a study by Caballero *et al*^[31], they reported that, micro and macro-vascular reactivity were markedly reduced in type 2 diabetic patients as well as impaired reactivity was present in relatives of type 2 diabetes patients and in subjects with impaired glucose tolerance.

Our study results showed a significant improvement in the brachial artery diameter change in response to reactive hyperemia (7.72 ± 3.4 Vs. $5.27 \pm 2, p < 0.05$, post fasting Vs. pre-fasting, percent increase in brachial artery diameter, mean \pm SD).

There is a life style modification during fasting in the month of Ramadan. Muslims fast from dawn to sunset (they neither eat nor drink). They have two meals per day (Iftar at sunset and Sohor before dawn). They exert more physically during the usual five prayers plus the added prayers specific for the

Ramadan. This adds up to an average of two hours per day. They also walk five times to the mosque which adds to the physical activity.

Hamdy *et al*^[32] studied the effect of life style modification on the improvement of endothelial function in obese subjects with the insulin resistance syndrome through the effect of a six month weight loss program and reported that this intervention significantly improved flow-mediated dilatation in the brachial artery ($12.9 \pm 1.2\%$ Vs $7.9 \pm 1.01\%$, final Vs. baseline respectively, $p < 0.0001$) with a linear relationship with percentage weight reduction.

This is in agreement with our study results, wherein our intervention (fasting during Ramadan) significantly improved the flow mediated dilation in brachial artery and showed a linear relationship with reduction in the waist circumference in both the male and the female group (94.68 ± 11.01 Vs. 92 ± 10.7 , $p < 0.0001$ and 89.76 ± 17.52 Vs. 87.18 ± 17.53 , $p < 0.0001$ respectively). The effect of Ramadan fasting on the waist circumference in males and females, as a reflection of abdominal adiposity, was in agreement with Soliman N^[33], Azizi F^[34] and Takruri HR^[35], who reported a significant decrease in body weight during Ramadan fasting. The decrease in body weight was due to efficient utilization of body fat during fasting. El-Ati *et al*^[36] reported that overweight persons lose more weight than normal or underweight subjects during the Ramadan.

As inflammation began to be recognized as a major contributor to the pathogenesis of atherosclerosis, cardiologists started to ask whether markers of inflammation could be used to predict the clinical outcome. Our study results revealed that fasting during the Ramadan significantly reduces the level of hs - CRP (0.26 ± 0.07 Vs. 0.48 ± 0.13 , $p < 0.001$ post fast Vs pre-fast, mean \pm SD) and shows a linear relationship with improved percentage FMD in the brachial artery.

These findings compare well with the study of Pasceri *et al*^[4] who studied the direct pro-inflammatory effect of CRP in human endothelial cells, and reported that CRP has a significant pro-inflammatory effect in both umbilical vein and coronary artery endothelial cells, inducing high levels of expression of ICAM-1, VCAM - 1 and E-selectin.

Our findings compare well with the results of Ridker *et al*^[11], who reported that even small increments in serum levels of CRP are associated with higher risk of atherosclerosis and ischemic heart disease in apparently healthy subjects.

Lowering of CRP levels may have beneficial effect on the evolution of atherosclerosis and may reduce the risks of coronary events. In our study, this was achieved with a non-pharmacological intervention (Ramadan fasting). Ridker *et al*^[38]

found that the reduction of serum CRP by statins was associated with a better clinical outcome after acute myocardial infarction.

CONCLUSION

We observed that fasting during the Ramadan had a favorable effect on endothelial function. It also reduced the direct pro-inflammatory effect of CRP on human endothelial cells as well as waist circumference which is a measure of abdominal adiposity. Hence, Ramadan fasting can affect the link between atherosclerosis, inflammation and adiposity with a non-pharmacological intervention in type 2 diabetes.

These favorable effects have occurred in spite of the short period of fasting (29-30 days per year). We, therefore, suggest that a systematic fasting of one to two days per week even after the Ramadan period would serve as an excellent part of healthy lifestyle.

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Case Report

Coronary Artery Ectasia: A Case Report and Review of Literature

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ABSTRACT

Coronary artery ectasia is not an uncommon diagnosis and is well described in the literature in large-scale reports. Two patients presented with chest pain and positive stress ECG test for reversible ischemia. Coronary angiogram

showed coronary artery ectasia with no obstructive coronary artery disease. Only medical treatment was recommended.

KEY WORDS: atherosclerosis, coronary angiography, coronary artery ectasia

INTRODUCTION

Ectasia is characterized by irregular, diffuse, saccular or fusiform dilatation of the coronary arteries, which may be isolated or coexist with concomitant obstructive coronary artery disease^[1]. Coronary artery ectasia with or without concomitant obstruction may occasionally be found in association with angina pectoris^[2]. The frequency of this finding is an infrequent diagnosis and is estimated to be between one and 2.5%^[2].

Case 1:

A 52-year-old male presented with effort-induced retrosternal chest pain and referred to left shoulder, with functional class II angina (Canadian classification). He had a 10-year history of hypertension and 12 years of hypercholesterolemia. He had no history of diabetes mellitus, nor family history of coronary artery disease. His pulse rate was 87/minute and blood pressure was 150/85 mmHg. Electrocardiogram was within normal limits.

Laboratory investigations results were as follows: hemoglobin: 14 g/dl, total cholesterol: 6.7 mmol, triglycerides: 2.4 mmol, uric acid: 387 mg and fasting blood sugar: 5.4 mmol.

Transthoracic echocardiography revealed mild left ventricular hypertrophy, normal left ventricular systolic function, EF=58% and diastolic dysfunction. No segmental wall motion abnormalities were noticed. Pulsed tissue Doppler imaging revealed regional systolic and diastolic dysfunction at the anterior septum and the anterolateral segments.

Treadmill exercise ECG test using Bruce protocol revealed positive stress test for reversible myocardial ischemia as there was a flat ST-segment depression of more than 1 mm in V3, V4, V5 after 0.80 second from J point.

Coronary angiography revealed saccular dilatation of proximal segment of left anterior descending coronary artery up to second septal perforator with luminal diameter = 9 mm and luminal diameter of distal artery = 2.4 mm (Fig. 2). There were no obstructive lesions in coronary arteries but there was a slow flow in the distal coronary artery.

The patient was started on clopidogrel tablets once daily for six months, ASA tablets 150 mg once daily, ACE inhibitor tablets 5 mg once daily and statin tablet once daily 10 mg.

Case 2:

A 54-year-old male presented with effort-induced retrosternal chest pain. There was no history of effort induced shortness of breath, no orthopnea nor paroxysmal nocturnal dyspnea. He had a 10-year history of hypertension and a five year history of hypertriglyceridemia. There was no personal or family history of diabetes mellitus. His pulse rate was 92/minute and blood pressure was 130/65 mmHg. ECG was within normal limits.

Transthoracic echocardiography revealed mild left ventricular hypertrophy, normal left ventricular systolic function, EF=62% and diastolic dysfunction. No segmental wall motion abnormalities were

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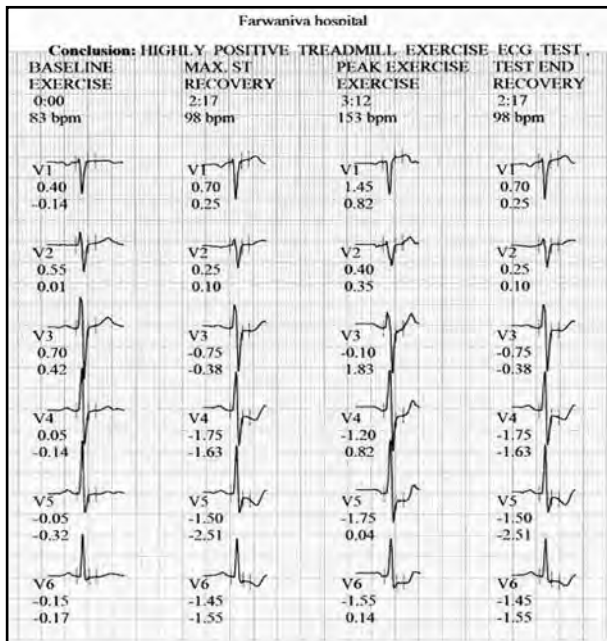


Fig. 1: Treadmill exercise ECG test for case 1, showing positive test for reversible ischemia

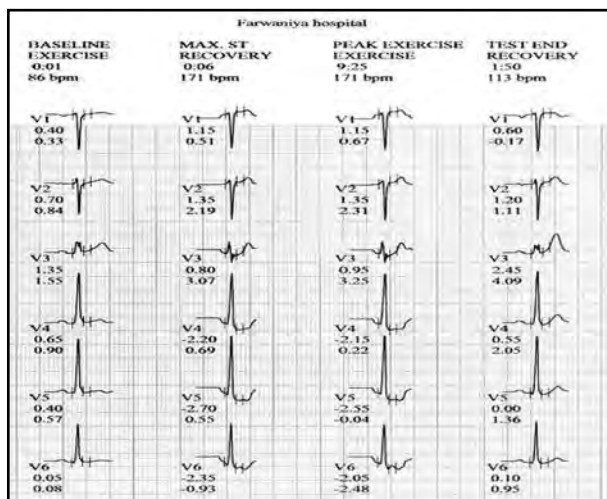


Fig. 3: Treadmill exercise ECG test for case 2, showing positive test for reversible ischemia

noted. Pulsed tissue Doppler imaging revealed regional systolic and diastolic dysfunction at anterior septum and anterolateral segments.

Treadmill exercise ECG test by Bruce protocol revealed positive stress test for myocardial ischemia as there was flat ST-segment depression > 2mm in II, III, aVF, V5, V6 (Fig. 3).

Coronary angiography revealed saccular dilatation of proximal segment of left anterior descending coronary artery up to second septal perforator with luminal diameter = 7 mm and luminal diameter of distal artery = 1.4 mm, saccular dilatation of proximal segment of left circumflex coronary artery up to posterior coronary artery of left ventricle with luminal diameter = 6.8 mm and luminal diameter of distal artery = 1.2 mm. No obstructive lesions in coronary arteries were



Fig. 2: Coronary angiogram for case 1, showed coronary ectasia at left main, proximal LAD

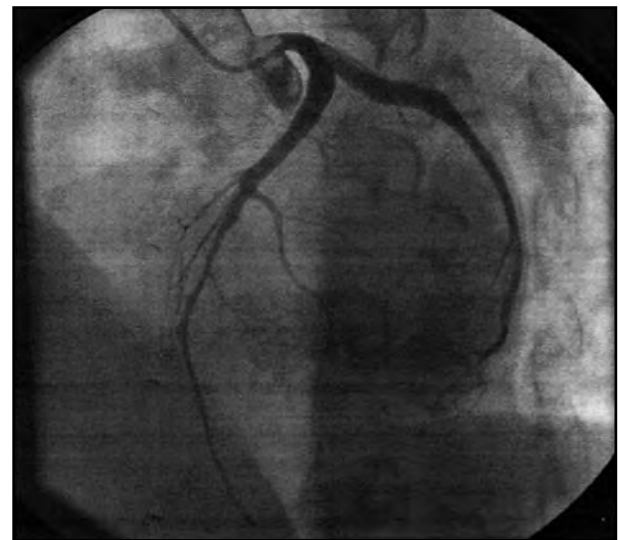


Fig. 4: Coronary angiogram for case 2, showed coronary ectasia at left main, proximal circumflex and proximal LAD

noticed. There was a slow flow in distal coronary artery. The dominant right coronary artery had diffuse dilatation with no coronary collaterals (Fig. 4, 5).

The patient was put on clopidogrel tablets once daily for six months, ASA tablets 150 mg once daily, ACE inhibitor tablets 5 mg once daily, statin tablet once daily 10 mg and metoprolol 50 mg once daily.

DISCUSSION

Since the description by Morgagni of coronary arterial dilatation in a patient with syphilitic aortitis^[3], isolated antemortem cases of ectasia or aneurysms of the coronary arteries have been described as a probable isolated congenital lesion^[4] or in association with congenital heart disease^[5], Ehlers Danlos syndrome^[6], polyarteritis^[7], bacterial infection^[8] and atherosclerosis^[9]. Scott^[10] collected a series of reported cases of aneurysms and he found that the most common type was of congenital



Fig. 5: Coronary angiogram for case 2, showed diffuse coronary ectasia of right coronary artery

origin and that the mycotic-embolic type was next in frequency.

In a consecutive series of 694 autopsies with detailed examination of the coronary arteries, Daoud *et al* in 1963^[11] found in patients over age 16 years, a prevalence rate of 1.4 percent of localized saccular and fusiform atherosclerotic dilatations of the coronary arteries, which he called aneurysms. An aneurysm is a sac that must be distinct from the remainder of the vessel to be appreciated. Markis *et al* in 1976^[12] preferred the word ectasia, since the entire vessel, throughout its course, can be involved and term is descriptive of the anatomic features. The diagnosis and therapeutic implications of this entity with its atherosclerotic origin can then be separated from the diverse group of cineangiographic and postmortem conditions that have previously been collectively termed aneurysms. They described four types of coronary ectasia: diffuse ectasia of two or three vessels was classified as type I, diffuse disease in one vessel and localized disease in another vessel as type II, diffuse ectasia of one vessel only as type III and localized or segmental ectasia as type IV.

Daoud *et al*^[11] described ten cases found at postmortem examination; all patients had severe atherosclerosis. Six patients had a history of hypertension but surprisingly, the cause of death in eight out of the ten was an abdominal aortic aneurysm. Benchimol *et al*^[13] observed only two cases of coronary arterial aneurysm of probable atherosclerotic origin in more than 2000 selective coronary cine angiograms.

Pathologic examination of coronary arteries revealed the typical diffuse hyalinization, lipid deposition, destruction of intima and media, focal calcification and fibrosis, cholesterol crystals, intramural hemorrhage and foreign body giant cell reaction of the atherosclerotic process. Once the process extended to the media, extensive

destruction of the musculoelastic elements was evident, resulting in marked attenuation of the vessel wall. In areas with relatively intact media, the ectasia was absent. The irregular and focal distribution of the process suggests that the ectasia, manifested angiographically as fusiform dilatations, is generated by intraluminal pressures against an elastic vessel wall with decreased stress tolerance^[14].

In 1985, Hartnell *et al*^[2] reported that coronary artery ectasia affects about 2% of the general population, but the aetiology of this coronary enlargement is unknown. One possibility is that there is an imbalance between the beneficial effects of nitric acid (NO) on coronary dilation and the potentially detrimental effects of chronic overstimulation by this endothelium-derived relaxation factor.

Many patients with angina receive chronic glyceryl trinitrate therapy. Yet no one has implicated an increased frequency of ectasia, as one might anticipate since this agent acts *via* NO stimulation. Perhaps the lack of ectasia is related to the mild doses used. Another possibility is that these patients usually have coronary artery disease, and atherosclerosis blunts the ability of the endothelium to produce adequate NO^[15].

The effect of atherosclerosis on NO production was shown by Quyyumi *et al*^[15]. They found that coronary vascular dilation in response to acetylcholine is predominantly caused by increased production of NO and that, despite the absence of angiographic evidence of atherosclerosis, patients with at least one known risk factor for coronary artery disease had reduced resting and stimulated bioavailability of NO from the coronary circulation. A paradoxical vasoconstriction has been seen in atherosclerotic vessels stimulated with acetylcholine. This may be related to the relation between NO-induced vasodilation and endothelin-induced vasoconstriction. When the reduced bioavailable NO is stimulated by acetylcholine, the contrasting action of endothelin becomes dominant and vasoconstriction could result^[16].

Several observations may help us to understand the aetiology of ectasia. England^[17] found an increased frequency or clustering of ectasia in a retrospective review of young men surviving a myocardial infarction in rural Australia. These individuals were farmers who had been exposed to herbicide sprays. Common components of most herbicides include 2, 4-D (dichlorophenoxyacetic acid), 2,4,5 -T (trichlorophenoxyacetic acid), or an acetylcholinesterase inhibitor. Extended exposure to these agents might lead to chronically raised concentrations of acetylcholine in the coronary interstitium. A possible mechanism is that 2, 4-D and

2,4,5 -T herbicides (containing acetic acid) increase acetylcholine concentrations through competitive inhibition by directly increasing the end products of acetylcholine breakdown, choline and acetic acid. Herbicides containing acetylcholinesterase inhibitors would directly increase the concentrations of acetylcholine.

Acetylcholine is a potent stimulator of NO^[18]. Therefore, herbicides may be responsible for locally increased NO concentrations. NO stimulates the relaxation of vascular smooth muscle via the guanylate cyclase pathway and release of calcium from the endoplasmic reticulum.

Lam and Ho from Singapore^[19] found the incidence of ectasia was 1.2% and the majority of patients were male in their sixth decade with underlying dyslipidemia or hypertension. They found coronary ectasia was associated with obstructive coronary artery disease in more than 80% of cases.

Akyurek *et al*^[20] from Turkey reported that coronary flow reserve is significantly reduced in patients with diffuse coronary ectasia. Although volumetric coronary blood flow is significantly higher in coronary ectasia, microcirculatory dysfunction that is reflected as depressed coronary flow reserve may be the underlying cause of exercise induced myocardial ischemia. The patients with isolated coronary artery ectasia have raised levels of plasma soluble intracellular adhesion molecule-1, vessel cell adhesion-1 and E-selectin in comparison with patients with obstructive coronary artery disease without coronary ectasia and control group with normal coronary arteries, suggesting the presence of a more severe and extensive chronic inflammation in the coronary circulation in these patients^[21].

Yetkin *et al*^[22] reported that the patients with coronary artery ectasia have an increased prevalence of varicocele compared to those with coronary artery disease and the mechanism underlying coronary artery ectasia might further increase the prevalence of varicocele in susceptible patients. The coronary artery ectasia / aneurysm may lead to exercise induced ischemia, especially in the diffuse form^[23]. Endoh *et al*^[24] reported that coronary ectasia is not benign and must be carefully monitored and coronary atherosclerosis may contribute to the occurrence of subsequent cardiac events.

Akdemir and his colleagues^[25] found that HLA-DR B1*13, DR 16, DQ2 and DQ5 genotypes may be associated with the pathogenesis and increased risk of coronary artery ectasia. The activation of the rennin angiotensin system may lead to an increased inflammatory response in the vessel wall or to an activation of matrix metalloproteinases and an insertion / deletion (ID) polymorphism of ACE has

been associated with development of aneurysm. They also found that an angiotensin converting enzyme DD genotype may be a risk factor for coronary artery ectasia^[26].

Pegel *et al* from Israel in 2002^[27] reported that coronary artery ectasia is associated with increased coronary spasm, dissection and thrombus formation. However, its relative contribution to coronary morbidity remains unclear. The natural evolution of coronary ectasia in the patient who was treated with ligation of aneurysm and distal bypass grafting under cardiopulmonary bypass revealed that a fragile fresh clot was formed within the aneurysm irrespective of coumadin therapy as a standard regimen for the coronary artery ectasia^[28].

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Case Report

Aortic Stenosis and Pregnancy: A Case Report and Review of Peripartum Anesthetic Management

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ABSTRACT

Pregnancy and the peripartum period represent a physiological burden for the patient with aortic valve stenosis. Maintaining cardiovascular stability with optimal hemodynamic parameters and adequate systemic perfusion pressure during the anesthetic management of patients with aortic stenosis can be extremely challenging.

Although epidural regional anesthesia for delivery and labor is traditionally contraindicated in these patients, we report a successful and uncomplicated epidural anesthesia in a patient with severe aortic stenosis scheduled for elective induction of labor.

KEYWORDS: anesthesia, aortic stenosis, epidural, pregnancy

INTRODUCTION

Patients with aortic stenosis are at risk of increased morbidity and mortality when undergoing anesthesia^[1]. Aortic stenosis during pregnancy is mostly due to congenital etiology^[2]. There is considerable debate as to the optimal anesthetic management of these patients for cesarean section, with some recommending the careful use of a regional technique^[3], whilst others argue that general anesthesia is preferred^[4]. The choice of anesthetic should be appropriate to the well-being of both mother and fetus. We report the use of titrated epidural regional anesthesia in conjunction with assisted second stage of labor facilitating stable hemodynamics and smooth vaginal delivery in a patient with severe aortic stenosis.

CASE REPORT

A 31-year-old woman (gravida 2, para 1) presented to the anesthesia preadmission clinic at our tertiary care obstetric hospital at 38 weeks gestation. The patient was diagnosed with aortic stenosis since five years of age. Prior to conception she had been reviewed by a cardiologist and at that time she had no cardiac-related symptoms or other health problems. There were no reported documents of echocardiography prior to conception. Three years previously, the patient had an uneventful pregnancy, with spontaneous vaginal delivery at term under epidural regional anesthesia. She had no cardiac symptoms during that pregnancy or during parturition, and there was no documentation of the severity of her aortic valve disease at that time.

The current pregnancy had progressed uneventfully except for intermittent history of increasing dyspnea beginning in the second trimester. When reviewed by the cardiologist at 32 weeks gestation, she was noted to have a systolic ejection murmur graded 6/6 at the second left intercostal space radiating to the neck. She was normotensive and in sinus rhythm. At that time the patient had no clinical symptoms of aortic stenosis. She was not on any regular medications and had no reported allergies. Echocardiography was performed at the same visit, which showed left ventricular hypertrophy with an aortic valve area estimated to be 0.7cm² and a pressure gradient across the valve estimated to be 88 mmHg. A multidisciplinary conference involving cardiology, anesthesiology and obstetrics was held to determine the most appropriate management of this patient. As the patient had requested epidural anesthesia for labor, it was felt that elective induction at 39 weeks preceded by an epidural regional anesthetic would allow precise titration of local anesthetic to effect and thereby minimize physiological changes.

At 39 weeks gestation, patient was admitted to the obstetrical triage unit. At that time, she was in sinus rhythm, normotensive and had no signs or symptoms of cardiac failure. The options for analgesia during labor and delivery, as well as for anesthesia for cesarean section should that become necessary, were discussed in detail with the patient. Risks and benefits were described. She requested epidural analgesia for labor and delivery, and an informed consent was obtained. Following an overnight fast

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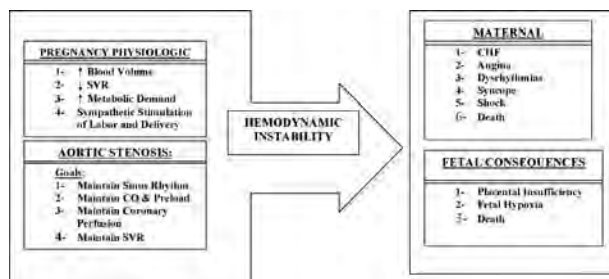


Fig. 1: Factors directly affecting myocardial performance, cardiac output, and systemic perfusion pressure with aortic stenosis are shown in *italics*. These factors must be optimized to maintain or increase flow across the stenotic aortic valve in order to avoid unwanted maternal and fetal consequences. CHF = congestive heart failure; CO = cardiac output; SVR = systemic vascular resistance.

and routine gastric acid prophylaxis, the patient was transferred to the delivery suite anesthetic room. Cardiotonic medications and equipment for resuscitation including the placement of a central venous catheter were immediately available. An 18 gauge cannula was inserted under local anesthesia for intravenous access followed by an insertion of radial arterial line (using Arrow QuickFlash®) for hemodynamic monitoring. An invasive arterial pressure was measured continuously from this point and baseline of blood pressure at this time was 105/55 mmHg. Since the patient was asymptomatic at the time of her presentation for induction of labor, it was felt that central venous access was unnecessary. Pulse oximetry and ECG monitoring were also employed.

With the patient sitting upright and under aseptic conditions, the skin was infiltrated with 1.5 ml of 1% lidocaine followed by insertion of a 17 gauge Tuohy epidural needle at the L2/L3 interspace. Following identification of the epidural space using the loss of air resistance technique, a 20 G nylon epidural catheter (Portex®) was passed four cm into the epidural space and the Tuohy needle was removed. The catheter was secured in place. Following negative catheter aspiration for blood and CSF, a test dose of 3 ml of 1% lidocaine was injected through the catheter. After excluding an intrathecal block by the absence of motor block in the lower extremities, the patient was moved into the supine position with moderate left lateral tilt to avoid aortocaval compression. Oxygen was administered through a face mask at 5 l/min and continuous fetal heart rate monitoring was employed. The epidural catheter was then connected to an infusion pump, and an infusion of 0.125% bupivacaine and 2 µg/ml fentanyl was initiated at a rate of 6 ml/hr.

The level of anesthesia was titrated slowly over 60 minutes to T10 as assessed by loss of sensation to pin prick with careful monitoring of the patient's cardiovascular parameters. No changes were observed as the block was established. The obstetrical team then proceeded with elective

artificial rupture of membranes followed by the initiation of an oxytocin (syntocinon) infusion. The patient remained pain free and hemodynamically stable throughout the first stage of labor. To avoid the cardiovascular stress associated with pushing and straining in the second stage of labor, a forceps delivery was planned. When the cervix was fully dilated and all the prerequisites for a forceps delivery were met, they were applied to assist in a smooth vaginal delivery. A 4150 g female infant who had Apgar scores of 9 and 9 after 1 and 5 min, respectively, was delivered vaginally with no complications. Following delivery, the patient remained under observation in the intensive care unit (ICU) with continuous arterial blood pressure, pulse oximeter, and ECG monitoring for 24h. No cardiovascular sequelae were reported, and her postpartum course was uneventful.

DISCUSSION

The main anesthetic considerations in patients with aortic stenosis include the consequences of a relatively fixed cardiac output and left ventricular hypertrophy with vulnerability to myocardial ischemia. These problems are further compounded by the normal cardiovascular changes occurring in pregnancy and at delivery. The cardinal manifestations of aortic stenosis include syncope, angina pectoris, and dyspnea. Once these symptoms develop, the prognosis is poor. The onset of angina, syncope, and dyspnea has been shown to correlate with an average time to death of five, three and two years, respectively^[5].

Pregnancy is associated with normal physiological changes that have important consequences on hemodynamics in patients with underlying heart disease^[2]. A 50% increase in intravascular volume occurs during normal pregnancy by mid third trimester. There is 50% increase in cardiac output, mainly in the first and second trimesters, the level peaks by about 24 weeks of pregnancy. Later, the increase in cardiac output is sustained by an increase in heart rate. The requirements for an increase in cardiac output and heart rate can lead to decompensation in patients with aortic stenosis.

During labor, cardiac output increases by a further 45% above the pre-labor level. With each contraction, up to 500ml of blood is displaced from the uterus into the circulation. After delivery of the baby, caval compression is relieved, and after the placenta is delivered, another auto-transfusion occurs from the placenta into the maternal circulation. Both will increase the cardiac output and stroke volume by about 80%. Thus the periods of greatest risk for cardiac events during pregnancy are early third trimester, during labor and delivery and immediately postpartum^[6].

Doppler assessment is commonly used to evaluate the severity of valve lesions. This assessment is difficult during pregnancy, since it is unclear how pressure gradients change during pregnancy with either normal or abnormal heart valves. Lesniak-Sobelga *et al*^[7] showed that the aortic valve gradient was greater by 20-35 mmHg during the antepartum period as compared to during postpartum. Thus in the absence of appropriate studies, the clinical significance of increased systolic gradient across the aortic valve cannot be assumed to be the same in pregnant and non-pregnant patients.

Severe aortic stenosis is poorly tolerated during pregnancy. Patients who are symptomatic or who have a peak outflow gradient of more than 50 mmHg are advised to delay conception until after surgical correction^[8]. Case series of women with an aortic stenosis have shown that pregnancy is well tolerated when the patients were asymptomatic before becoming pregnant. In patients with mild or moderate aortic stenosis (valvular opening area 1.0-1.5 cm²) no cardiac complications were observed during pregnancy, while cardiac events were observed in 10% of all women with significant aortic valve stenosis (valvular opening area < 1.0 cm²). Patients predominantly delivered vaginally under regional analgesia and in some cases with surgical assistance. With one exception, cesarean sections were carried out exclusively for obstetric indications^[9].

The goals of anesthetic management for patients with aortic stenosis are as follows: (A) to avoid both tachycardia and bradycardia; (B) maintain adequate preload in order that the left ventricle may generate an adequate cardiac output across the stenotic valve; (C) maintain intravascular volume and venous return (avoiding aortocaval compression); and (D) avoid myocardial depression during anesthesia (see Fig. 1). Historically, anesthesiologists have avoided spinal and epidural anesthesia in the parturient with aortic stenosis because of the possible adverse cardiovascular changes in a patient with a fixed cardiac output. The sympathetic block from these techniques can result in decreased venous return and preload, with potentially catastrophic results on cardiac output. Moderate-to-severe aortic stenosis remains a relative contraindication for single-shot spinal anesthesia. However, numerous reports have described the safe use of continuous epidural or continuous spinal anesthesia for vaginal or cesarean delivery in women with aortic stenosis^[10,11].

CONCLUSION

In conclusion, all the arguments for and against these techniques are based on anecdotal case reports and assessment of theoretical risks. Multidisciplinary antenatal care of these women is important and should involve obstetrician, anesthesiologists and cardiologists. Regular assessment of cardiac function is essential. The anesthetic plan for delivery should include provision for the use of invasive monitoring throughout labor and delivery and for high-dependency postpartum care. Regional anesthesia has significant risks, but incremental induction of either continuous epidural or continuous spinal anesthesia should be considered for labor analgesia. These techniques are also reasonable alternatives to general anesthesia for cesarean section in the parturient with aortic stenosis.

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Case Report

A Case of Gitelman's Syndrome Presenting with Hypocalcemia

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ABSTRACT

Gitelman's syndrome (GS) is an autosomal recessive disorder caused by a defect of the thiazide-sensitive Na-Cl cotransporter (TSC) at the distal tubule, characterized by hypomagnesemia, hypokalemic alkalosis and hypocalciuria. This condition was previously confused with Bartter's syndrome (BS). The documentation of

hypocalciuria helps to differentiate this syndrome from BS. We report a 35-year-old female patient presented to our hospital with a history of muscle weakness and carpal spasm. She showed hypokalemia, hypocalcemia, hypomagnesemia and hypocalciuria. She was treated with electrolyte supplements.

KEY WORDS: autosomal recessive disorder, hypocalcemia, renal disorder

INTRODUCTION

Gitelman's Syndrome (GS) is an inheritable renal disorder characterized by hypomagnesemia, hypokalemia and hypocalciuria. Patients usually present at an older age and have mild clinical picture and normal or slightly decreased concentrating ability. GS is caused by a defect in NaCl transport in the distal convoluted tubule^[1-4]. The diagnosis of GS can be made on the basis of clinical features, laboratory data and renal function test. The treatment is usually to correct electrolyte imbalance^[4]. The objective of this study is to report the first case of GS in Kuwait which presented with symptoms and signs caused by hypocalcemia.

CASE REPORT

A 35-year-old female patient presented with a two week history of malaise, diffuse muscle pains and weakness, leg cramps, diarrhea, vomiting, polyuria and carpal spasm. These symptoms were recurrent over the last four years. She denied any form of self-medication, surreptitious diuretic and laxative abuse, persistent vomiting and diarrhea and there was no history of chest problems. Past history as well as family history were unremarkable.

Physical examination revealed a lady of an average built. She was clinically euvolemic with normal skin turgor and no peripheral edema. Her blood pressure was 100/ 65 with no evidence of postural hypotension. She had clinical evidence of distal muscle weakness. The rest of the examination

was within normal limits.

Biochemical investigations revealed hypokalemia (s.K 2.9 mmol/l, normal values 3.6-5.1), hypocalcaemia (corrected s.Ca 1.9 mmol/l, 2.1-2.6), hypomagnesemia (s.Mg 0.3 mmol/l, 0.74-1.2), hypochloremic metabolic alkalosis (s.Cl 87 mmol/l, 94-115), pH 7.48 (7.35-7.45), HCO₃ 31 mmol/l (22-26), PO₄ 1.02 mmol/l (0.87-1.45), Alk phos 58 iu/l (42-98), serum albumin 39g/l (35-48), Hb 123 g/l (120-150), WBC 6.9 (4.0-12.0), platelet count 260 (150-400), creatinine 67mmol/l (53-97), BUN 2.9mmol/l (2.5-7.2), ALT 16 iu/l (10-60), AST19 iu/l (10-42), T. bil 9 umol/l (3-35) .

Urinalysis was normal with a pH of 6.8 and specific gravity of 1.013. Urine calcium/creatinine ratio was low 0.045 (0.08-0.57). 24 hour urine collection showed hypocalciuria (U.Ca 0.9 mmol/l, 1.5-5.5), hypermagnesuria (U. Mg 5.5 mmol/day, 3.0- 5.0) and hyperkaluria (U. K 148.6 mmol/day, 25-125). The plasma renin was increased at 83 mU/ l (7.0-76.0) with secondary hyperaldosteronism (s. Aldosterone 964 pmol/l, 111 - 862). Other investigations showed normal levels of PTH (3.7 pmol/l, 0.7-5.6) , 25 OH Vit D (52.1 nmol/l, 23-113) and no glucosuria.

Renal Ultrasound study was normal. Molecular genetic studies and urinary prostaglandins were not performed. The presence of hypokalemia, hypomagnesemia, hypochloremic metabolic alkalosis, hypocalciuria and hyperaldosteronism makes Gitelman's syndrome the most likely

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Table 1: Characteristics of Bartter's syndrome and Gitelman's syndrome (modified from Devendra and Rowe)^[6]

	Bartter's syndrome	Gitelman's syndrome
Age of presentation	Prenatal, during infancy or early childhood	Late childhood or at adulthood
Clinical features	Lethargy, failure to thrive, polyuria, polydypsia, vomiting, constipation, salt craving, dehydration, nephrocalcinosis, chondrocalcinosis	Weakness, abdominal pain, constipation, vomiting and tetany
Localization of defect	Ascending limb of Henle	Distal tubule
Biochemical differences	Serum magnesium may be decreased Urinary excretion of calcium increased or normal	Serum magnesium decreased Urinary calcium excretion reduced
Molecular differences	Na-K-2Cl transporter or apical K channel or basilar lateral Cl channel in thick ascending limb of Henle	Na-Cl cotransporter in the distal tubule
Furosemide test	No or little response	Shows a response
Thiazide test	Shows a response	No or little response

diagnosis. Hypocalcemia may have been secondary to hypomagnesemia. Despite the low corrected Ca, PTH level was normal as persistent hypomagnesemia impairs the synthesis and secretion of PTH^[1].

She was treated with magnesium and potassium supplements and potassium sparing diuretic. Serum potassium and magnesium levels were partially corrected to 3.0-3.2 mmol/l and 0.48 mmol/l respectively. Serum Ca was corrected to 2.03 mmol/l. However, the urinary excretion of the potassium and magnesium were still higher than normal. As the patient was planning to get pregnant, potassium sparing diuretic was stopped and she continued on magnesium and potassium supplements. The patient's symptoms were partially improved.

DISCUSSION

To best of our knowledge this is the first reported case of GS in Kuwait. Although GS is unlikely to present with hypocalcemia, our case is not the only case with such a finding. In 2005 there were two reported cases of GS associated with hypocalcemia^[2,3].

Gitelman's syndrome is an inherited renal disorder characterized by hypomagnesemia, hypokalemia and hypocalciuria. The diagnosis is usually made on the basis of clinical and biochemical findings. Patients are frequently asymptomatic or may present with transient episodes of weakness, abdominal pain, constipation, vomiting, fever and tetany. Disease-free intervals may be prolonged resulting in delay in diagnosis until adulthood^[4].

The outstanding biochemical findings in GS are hypomagnesemia and hypocalciuria. Hypokalemia and mild to moderate metabolic alkalosis are usually present but their presence is not necessary to establish the diagnosis. Urinary calcium in affected patients is usually below 2.0 mg/kg body weight per day and the urine calcium/creatinine is less than 0.1^[5].

This condition was previously confused with Bartter's syndrome (BS). Some of the features that

help to differentiate the two conditions are shown in Table 1 (modified from Devendra and Rowe)^[6].

The documentation of hypocalciuria, hyperkaliuria and hypermagnesuria helps to differentiate this syndrome from BS which is associated with nephrocalcinosis^[7] and chondrocalcinosis^[8]. The pathophysiology of GS has been clearly outlined by Bhandari^[9]. There is Na-Cl wasting and hypovolemia which stimulates the renin-angiotensin-aldosterone system and causes an increase in apical Na⁺ reabsorption and stimulation of the basolateral Na⁺/K⁺-ATPase. The increased aldosterone levels also stimulate cortical and medullary collecting ducts H⁺/ATPase pumps leading to an increased apical H⁺ ion secretion. K⁺ and H⁺ ion excretion increases as K⁺ enters from the basolateral membrane via the Na⁺/K⁺-ATPase pumps resulting in hypokalemic metabolic alkalosis. The resultant low intracellular Na⁺ increases distal convoluted tubule Ca²⁺ reabsorption via basolateral Na⁺/Ca²⁺ exchangers causing hypocalciuria. Mg²⁺ loss via apical Mg²⁺/Na⁺ exchangers increases due to the net negative transepithelial potential. Hypermagnesuria may be caused also by associated hypokalemia^[10], metabolic alkalosis^[11] or low renal Mg threshold^[12]. Hypomagnesemia and hypocalciuria may also occur following the administration of thiazide diuretics which inhibit the distal luminal Na-Cl cotransporter. The combination of hypokalemia and hypocalciuria is also a feature of cis-platinum toxicity^[13]. Patients also show an increase in potassium concentration in the sweat^[14].

Hypomagnesemia results in failure of repletion of cellular potassium stores due to urinary losses. The resulting hypokalemia is refractory to treatment with potassium salts alone and its correction requires the prior or simultaneous correction of Mg deficiency^[15]. The poor absorption of magnesium and its high urinary excretion in patients with GS may explain why some patients do not respond to magnesium supplement^[16]. Normalization of serum magnesium may be difficult to achieve since

high doses of magnesium may cause diarrhea. All magnesium salts have been used but MgCl_2 is preferred because it compensates for urinary Cl loss^[12]. Each milliliter of the 5% solution contains 0.5 mEq (6 mg) of Mg^{++} . The total dose is individualized and given at 6 to 8 hour intervals. Potassium and prostaglandin inhibitors are usually not needed, although some patients may require potassium salts and/or anti-aldosterone medications such as amiloride or spironolactone to correct and maintain the serum potassium level^[17].

CONCLUSION

In conclusion, hypocalcemia could be considered as a feature of GS. In the absence of surreptitious diuretic intake, laxative abuse and persistent vomiting and diarrhea, the presence of hypomagnesemia, hypokalemic alkalosis, hypokalemia, hypocalcemia and hypocalciuria should raise the possibility of GS.

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Case Report

Rhabdomyosarcoma of the Urinary Bladder in an Adult

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ABSTRACT

Rhabdomyosarcoma (RMS) of the urinary bladder is extremely rare in adults. This report documents a case of an embryonal RMS in a 77-year-old man with hematuria in Kuwait. He declined radiotherapy after a transurethral

resection of the tumor but remained asymptomatic until his death from pre-existing cardiac disease eight months later. This is the second case of RMS of the urinary bladder diagnosed in an adult in Kuwait over a 30-year period.

KEY WORDS: adult rhabdomyosarcoma, hematuria, urinary bladder

INTRODUCTION

Rhabdomyosarcoma (RMS) in childhood is relatively common in soft tissue but infrequent in the urinary bladder^[1]. Literature review indicates that RMS of the urinary bladder is rare in adults^[2,3]. Between 1974 and 2003, six cases of RMS of the urinary bladder were registered in the Cancer Registry of Kuwait Cancer Control Center. Most patients (4/6) were in the 2-5 year age group. The remaining two patients were 16 and 45 years old respectively.

The objective of this report is to document a case of RMS of the urinary bladder in a 77-year-old Kuwaiti male. This brings to two, the total number of cases of urinary bladder RMS seen in adults in Kuwait over a 30-year period.

CASE REPORT

A 77-year-old male Kuwaiti was admitted in Al-Sabah hospital in January 2004 with a two-week history of frank hematuria, nocturia, frequency of micturition, pain in the penile shaft, dribbling and interruption of urine during micturition. His medical history revealed that he was a diabetic on medical treatment. He had undergone previous cardiac surgery rendering him a grade IV risk for surgery. Both physical and laboratory examinations were essentially normal. Both ultrasonogram (Fig. 1) and computed tomography (CT) of the pelvis (Fig. 2) demonstrated a huge bladder mass and a normal prostate gland. Subsequent cystoscopy detected a partly necrotic tumor on the dome of the

urinary bladder. Transurethral resection (TUR) of most of the tumor was done. The tumor base was fulgurated but not resected for fear of perforation. Initial outflow from irrigation was smoky but became clear after two days. Postoperative recovery in the Intensive Care Unit (ICU) was uneventful and patient was discharged home in good condition.

Five weeks after the initial surgery, another TUR of the tumor was done. The patient refused radiotherapy and chemotherapy but was asymptomatic until he died eight months later from his cardiac problems.

Pathology

The first specimen consisted of 98 gm of multiple pieces of gray brown tissue measuring 8 x 7 x 6 cm. The second weighed 26 gm and measured 7 x 7 x 1.5 cm. Microscopically, both showed a richly vascular tumor, which had reached the muscular coat and had extensive necrosis, hemorrhage and frequent mitosis. Most tumor cells had round to oval or elongated nuclei and a variable amount of cytoplasm (Fig. 3). They were positive for desmin (Fig. 4), but negative for leukocyte common antigen, cytokeratin, epithelial membrane antigen, chromogranin, synaptophysin and HMB-45. A pathological diagnosis of embryonal rhabdomyosarcoma was made.

DISCUSSION

Reports in English literature suggest that the present case is probably the oldest patient with



Fig. 1: Preoperative U/S showing huge urinary bladder tumor located at the dome

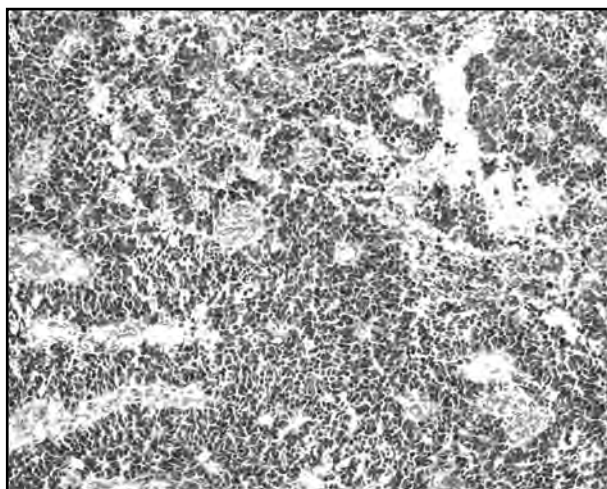


Fig. 3: Malignant small round cell tumor (H & E X 100)

RMS of the urinary bladder. Also, there is evidence that unrecognized urinary bladder RMS can disseminate^[4]. In the present case, the tumor was confined to the bladder wall.

The paucity of reported cases of RMS in literature attests to its rare occurrence.

This rarity has not facilitated the establishment of a uniform staging or treatment protocol. While some have been successfully treated by TUR, others have had total cystectomy and chemotherapy. Remarkably, Henriksson *et al* successfully managed a large RMS of the urinary bladder in a 56-year-old woman by TUR^[5,6]. Age, co-existence of other diseases, especially in elderly patients, and extent of the disease may influence choice of treatment modality. In the present case, age and pre-existing cardiac problems were limiting factors in the choice of TUR as the only treatment modality.

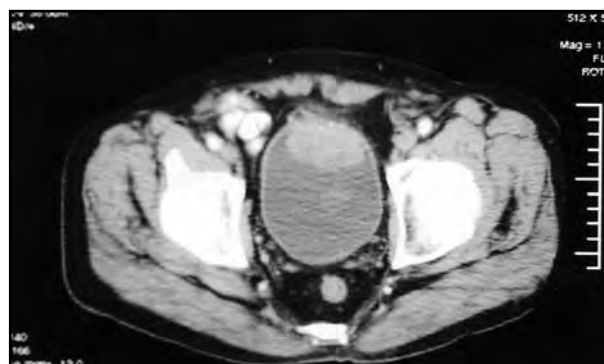


Fig. 2: Preoperative CT scan showing huge urinary bladder tumor located at the dome

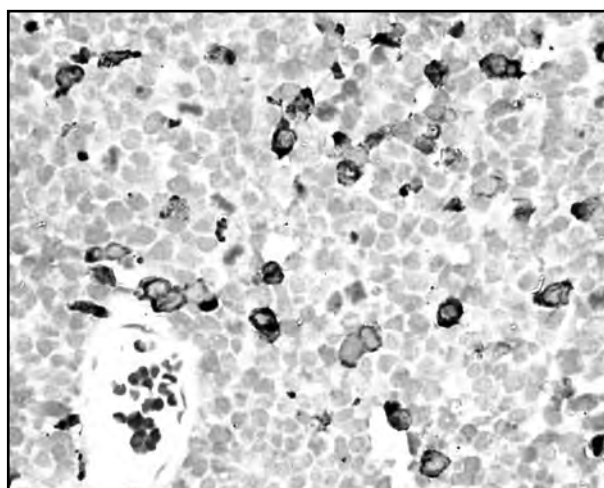


Fig. 4: Scattered cells are positive for desmin (Immunoperoxidase X 200)

Unfortunately, the effectiveness of this could not be evaluated, since the patient died eight months later from his cardiac problems.

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Case Report

Splenogonadal Fusion in a Boy: Case Report and Review of literature

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ABSTRACT

We report an unusual case of splenogonadal fusion in a four-year-old boy with history of bilateral undescended testes. He had presented to us when he was one month old with an empty scrotum. On clinical examination he had bilateral undescended testes. The right testis was palpable in the inguinal region and the left was not palpable. No other anomaly was detected on clinical examination. Right orchidopexy was done at three years of age. Left impalpable testis was subsequently managed by left groin exploration which revealed no testis. Hence exploratory

laparotomy was done. An intrabdominal left testis was found which had two abnormal-looking fleshy masses on its superior pole. Excision biopsy of these nodules was done and first stage orchidopexy was performed as it was difficult to mobilize the testis up to the left scrotum. Biopsy of the nodules revealed splenogonadal fusion; hence we were justified in saving the testis. Second-stage orchidopexy was done after three months to fix the testis in the left scrotum.

KEY WORDS: impalpable, intraabdominal, splenogonadal fusion, testis

INTRODUCTION

Splenogonadal fusion is a rare congenital anomaly, which is defined as an abnormal connection between the spleen and gonad or derivatives of mesonephros. It was first described by Boestrom in 1883 and later reported in detail by Pommer in 1989^[1].

It occurs most commonly in the left gonad in males. To date, approximately 150 cases have been reported in the literature. Preoperative diagnosis is possible only in a few cases and unnecessary orchidectomy is often performed because of suspicion of neoplasm^[2]. Cryptorchidism has been associated with splenogonadal fusion^[3]. We report a case of a child with an impalpable left testis with splenogonadal fusion and review the relevant literature.

CASE REPORT

A one-month-old boy was referred to us because of an empty scrotum. On clinical examination he had bilateral undescended testes with right palpable and left impalpable testis. He had a normal phallus and no other anomaly was noticed on clinical examination. An ultrasound examination showed normal-sized right testis in the inguinal canal but

the left testis was not found in the groin or abdomen. He was advised to undergo right orchidopexy first at one year of age but he did not come back to us till he was three and half years old. Right orchidopexy was planned first and normal-sized right testis was fixed in the scrotum. Three months later, left groin exploration by transverse crease incision was done. The left testis or cord structures were not present in the inguinal canal; hence incision was extended laterally and the abdominal cavity was entered after opening the peritoneum. The left testis was present in the peritoneal cavity deeper to the internal inguinal ring. It looked abnormal because of two fleshy masses on its superior pole. The first nodule was discrete and 1x1 cm size, attached to the cord in close proximity with the superior testicular pole. The second nodule diffusely merged with the superior pole of the testis near the head of epididymis. A suspicion of malignancy was considered intraoperatively on gross examination but it was decided to wait for the biopsy report to avoid unnecessary orchidectomy. The first nodule was excised without damage to any cord structure. Longitudinal excisional biopsy of the second nodule was done so as to include adjacent normal-looking testicular tissue. The testis was mobilized on its cord

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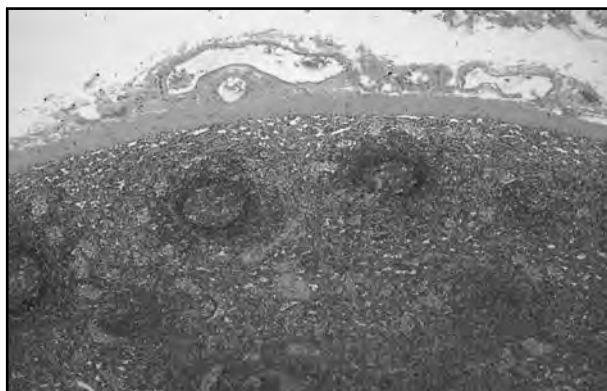


Fig. 1: Nodule on the upper pole of the testis comprising of ectopic spleen. (Hematoxylin and Eosin stain, 4 X)

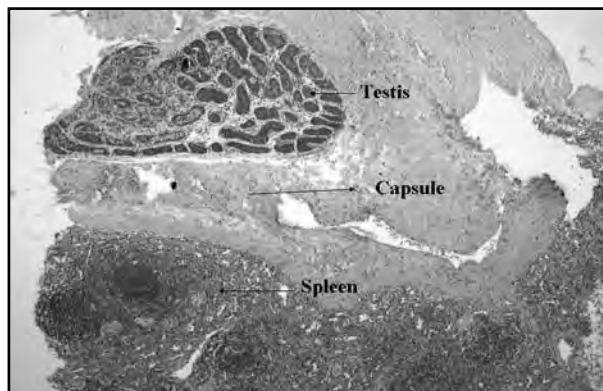


Fig. 2: Upper pole of left testis showing splenogonadal fusion. (Hematoxylin and Eosin stain, 4 X)

but it was not possible to bring it into the scrotum. Hence staged orchidopexy was planned and the left testis was fixed to the pubic tubercle. Histopathology report of the nodules came as splenogonadal fusion. The first nodule showed only ectopic splenic tissue (Fig. 1). The second nodule biopsy showed splenic and testicular tissues merging with each other by their capsules; hence a diagnosis of splenogonadal fusion was made (Fig. 2). Orthotopic spleen was normal and it was shown on subsequent ultrasound. Second stage orchidopexy was done three months later. The testis could be brought to the left scrotum this time without any tension. Both testes were well felt in the scrotum, on follow up visits.

DISCUSSION

Splenogonadal fusion is a rare entity. Several clinical reviews of this disorder have been published in the literature. It has been traditionally classified into continuous and discontinuous types^[4]. In the continuous type there is a direct connection between the principal spleen and gonad; the discontinuous type lacks any anatomical connection between ectopic spleen and native spleen. Both types occur with relatively equal frequency^[1]. Cryptorchidism is the most commonly associated anomaly involving 31% cases of splenogonadal fusion out of which 59% had bilateral undescended testes^[3]. The continuous type may be associated with other congenital anomalies like limb malformations, micrognathia, cardiac defects, cleft palate, anal anomaly, craniosynostosis and spina bifida. This reflects an embryological insult occurring between the 5th to 8th weeks of gestation^[5]. Although the exact etiology of splenogonadal fusion remains unknown, the most widely accepted etiology relates to events between the 5th and 8th weeks of gestation. Between five and six weeks of gestation splenic anlage forms in the dorsal mesogastrium. At the same time the gonadal ridge is formed between the dorsal mesogastrium and mesonephros on either side. As the stomach rotates to the left, splenic anlage also rotates and

lies in close proximity with the left gonadal ridge. Simple adhesion^[6] or mild inflammation^[7] between splenic tissue and gonad at this stage explains left presentation of splenogonadal fusion. The fact that in most cases the splenic capsule is intact supports the theory of simple fusion. It does not explain rare cases of right sided splenogonadal fusion^[6], intraovarian^[8] or intratesticular splenic tissue^[2].

Splenogonadal fusion occurs predominantly in males with a male- to- female ratio of 16:1. Out of 150 cases reported till now there were only 9 females; however, incidence in females could be underestimated because of inaccessibility of the female gonad to physical examination^[9]. This disorder can present at any age from birth to 80 years although the majority (82%) are below 30 years. Nearly half present below 10 years of age^[1,10]. Most commonly, this entity is an incidental discovery during routine groin exploration for an undescended testis or hernia^[10]. Approximately 17 % of reported cases were diagnosed at autopsy^[1]. Testicular swelling is the commonest presenting symptom. Another presentation is acute scrotal pain due to involvement of the ectopic spleen in various conditions like malaria^[11], torsion of splenic rest^[10], mumps, leukemia, mononucleosis^[12], traumatic rupture^[13] and bowel obstruction due to intraperitoneal cord of continuous splenogonadal fusion^[14]. Very rarely this condition is suspected or diagnosed preoperatively. Few imaging reports of this entity have appeared in the literature. Scintigraphy using agents labeled with technetium-99m has confirmed presence of splenic tissue in some reports^[15] and more recently radiologists have diagnosed this condition by ultrasound^[16, 17].

While no treatment is necessary when diagnosis is confirmed and no symptoms are present, in 37% of reported cases orchidectomy was done unnecessarily^[10]. There can be coincidental occurrence of testicular neoplasm in cases of splenogonadal fusion but till now no study has demonstrated a direct relationship between

splenogonadal fusion and development of testicular cancer^[18]. If surgical intervention is performed, orchidectomy is generally not indicated; splenic tissue usually can be dissected off the gonadal structures and the testis can be saved^[1, 10, 12, 13, 18].

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Case Report

Unilateral Maxillary Sinus Mucocele; Case Report and Review of Literature

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ABSTRACT

Paranasal sinus mucocèles are benign, locally expansile cyst-like masses that are lined by respiratory epithelium. Less than 1% of these involve the maxillary sinus. We

report the case of a 15-year-old female with a maxillary sinus mucocele who had undergone endoscopic left side antrochoanal polyp removal four times.

KEY WORDS: antrochoanal polyp, mucocele

INTRODUCTION

Paranasal sinus mucocèles are benign, locally expansile cyst-like masses that are filled with mucus and lined with respiratory epithelium^[1]. The majority are located in the frontal sinus (60%) followed by the ethmoid sinus (30%) and maxillary sinus (10%). They are rarely localized to the sphenoid sinus^[2]. The traditional treatment is excision or marsupialization. However, endoscopic intranasal approach has been recently introduced^[3]. The aim of this case report is to discuss the role of endoscopic approach in complex maxillary sinus mucocele.

CASE REPORT

A 15-year-old female, with complaints of intermittent bilateral nasal obstruction and rhinorrhea of one year duration, presented with complete nasal obstruction since the past three weeks. There was no history of epistaxis. Patient was a known case of recurrent left antrochoanal polyp for which she was operated for the first time at the age of nine years (2001).

At the age of eleven she was operated twice (four months apart) for a recurrent left antrochoanal polyp by simple intra nasal excision. One year later (2003) recurrence occurred on the same side and this was removed by endoscopic sinus surgery. No complications were reported with these surgeries. Her past medical history was otherwise unremarkable. She was not on any medications.

Histopathology reports of specimens from the initial three surgeries showed inflammatory polyps.

Examination of her right nasal cavity was unremarkable. Her left nasal cavity was completely filled with soft nontender mass that did not bleed on touch with an extension that completely occupied the nasopharynx. This was confirmed by a flexible naso-endoscope passed through the right nasal cavity. Examination of the oropharynx, ears and neck was normal.

Previous radiological records were not available. Preoperative computerized tomography (axial, coronal) revealed a homogenous opacity in the left maxillary sinus with the mass extending backward to the nasopharynx (Fig. 1 & Fig. 2). Part of the medial wall of the maxillary sinus was absent, which could most probably be due to previous surgeries rather than the pressure effect of the mucocele. The other sinuses were unremarkable.

Surgical decompression and marsupialization of the mucocele cavity through an endoscopic approach were carried out in this case. Clear yellowish fluid was aspirated from the mass. The mass in the nasal cavity was then excised completely with microdebrider and left maxillary sinus cleaned of any remnant. Histopathology following this endoscopic sinus surgery showed inflammatory polyp with cystic lesion in maxillary sinus (mucocele). The patient had regular follow-up for one year and no evidence of recurrence was noted by diagnostic endoscopy. CT scan after three months showed bilateral clear sinuses including

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Fig. 1: Axial CT showing mass in the left nasal cavity extending backward to the nasopharynx

the left maxillary sinus with the same defect in the medial wall.

DISCUSSION

The term mucocele was introduced by Rollet in 1896 and Onodi gave the first histological description in 1901. Paranasal mucoceles are most frequently found in the frontal and ethmoid sinuses. Their incidence in the maxillary sinus is less common, having been reported in only 3 to 10% of cases^[2]. In a cohort of 118 mucoceles of the paranasal sinuses, less than 1% involved the maxillary sinus^[3]. In one series, mucoceles were bilateral in 4% of cases^[4]. Fifty percent of patients with mucoceles have a history of prior infection, 25% have a history of trauma and 10% have a prior allergic history^[2]. In a series of 16 patients with maxillary mucoceles, a previous history of surgery or injury to maxillary sinus was obtained in 12 cases. Most had done Caldwell-Luc procedure. Symptoms appeared 10 years postoperatively^[1,5]. In some cases, there is histological evidence of an increase in the number of secretory cells in the lining membrane; hypersecretion of mucus may be a contributory factor^[6]. One postulated mechanism of formation of maxillary sinus mucocele is the formation of fibrotic bands which separate the anterior wall and posterior walls, thus interfering with normal drainage^[1]. Mucoceles that develop following Caldwell-Luc operations are thought to form as a result of entrapped sinus mucosa in the line of the anterior antrostomy^[7]. Mucoceles in the pediatric population are rare, with a few and isolated cases published, with a mean age of 10 year, the youngest being 12 months old^[8,9]. An underlying pathology usually exist, and should be investigated. Cystic fibrosis was found in previously published cases^[10,11]. The symptoms of mucoceles are related to their expansion and subsequent pressure on and obstruction of surrounding anatomic



Fig. 2: Coronal CT showing opacity in the left maxillary sinus

structures. Frontal and ethmoid mucoceles are often associated with headaches and sometimes with visual disturbances. Maxillary sinus mucoceles are more typically associated with symptoms of nasal obstruction, although visual disturbances have been reported^[12]. Medial expansion of the wall of the maxillary sinus into the nasal cavity displaces the inferior turbinate and causes nasal obstruction. Superior expansion of the antrum into the inferior orbit can cause displacement of the orbital contents and visual changes. Downward displacement into the area of the alveolus can even cause loosening of teeth^[13]. Although mucoceles are benign, they can cause significant pathology as a result of their effects on surrounding vital structures of the orbit and skull base. In addition, local symptoms of sinusitis, nasal obstruction, and anosmia can occur^[6]. The typical radiographic appearance of mucoceles is a fully opacified sinus with evidence of rounded or ovoid expansion and bone erosion^[7]. CT in the axial and direct coronal planes is the optimum method of showing the bone expansion that occurs in mucocele formation. The bony outline becomes more rounded as the bone remodels in response to growing pressure within the sinus cavity^[14]. Magnetic resonance imaging is best reserved for mucocele formation secondary to sino-nasal tumors, because in these patients only the lining membrane of the mucocele will enhance after intravenous contrast^[14].

Treatment of paranasal sinus mucoceles, including complex ones, is managed endoscopically. Treatment has traditionally involved excision or marsupialization *via* an external approach. More recently, an endoscopic intranasal approach has been advocated^[13]. External approaches include the Lynch incision, the bicoronal incision for frontal sinus mucoceles and the gingivobuccal incision (Caldwell-Luc) for maxillary sinus mucoceles^[12]. The lining of the mucocele should not be removed

as it forms an ideal lining for the cavity^[15]. Laterally placed maxillary mucocoeles are not always accessible through a simple middle meatus antrostomy. In these cases, a combined approach (endonasal and gingivobuccal approach) is sometimes required^[12]. FEES offers a conservative, minimally invasive treatment of paranasal sinus mucocoeles, thus avoiding the inconveniences of different external approaches such as recurrence, postoperative morbidity and longer hospitalization^[12].

CONCLUSION

Paranasal sinus mucocoele in maxillary sinuses are still rare. In our case the cause was the previous multiple surgical trauma. Even though the patient had not undergone Caldwell-Luc surgery in the past, incomplete removal of the diseased mucosa and inadequate widening of the ostium during previous surgeries could have provoked recurrence of the polyp. Imaging with CT-scan and MRI allow the physician to rule out other lesions and meningocoeles. Endoscopic endonasal surgery is now the gold standard for the treatment of paranasal sinus mucocoele.

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Case Report

Appendicular Mucocele - A Case Report

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ABSTRACT

Appendicular mucocele by definition is a cystic dilatation of the appendiceal lumen by mucin accumulation. This is a rare lesion; its prevalence in appendectomy specimens being only 0.2 - 0.3%. It may be an outcome of various processes. Most important from the surgical point of view is the mucocele caused by mucinous cystadenoma and cystadenocarcinoma. Less commonly it could be

due to appendicolith, carcinoid *etc.* It is known to be associated with pseudomyxoma peritonei resulting from a rupture. It is therefore important to identify the disease process preoperatively and to plan a careful resection. We report here one case with surgical and histopathological confirmation.

KEY WORDS: appendix, imaging, mucocele

INTRODUCTION

Appendicular mucocele is a rare lesion. It is a descriptive term denoting an obstructive dilatation of the appendicular lumen by mucinous secretions. Mucinous cystadenoma and cystadenocarcinoma account for 60 - 70% of all mucoceles. Less common causes are retention cyst, mucosal hyperplasia, carcinoid, appendicolith, endometriosis, adhesions and volvulus. The clinical presentation is usually non-specific with 50% of cases being an incidental finding at surgery. Symptoms could be an indeterminate abdominal pain or chronic or intermittent abdominal colicky pain due to intussusception of the mucocele. Occasionally the patient could present with sepsis due to a superimposed infection.

CASE REPORT

A 26-year-old male presented with a mass in the right lower quadrant of the abdomen. He had felt the mass two months prior to presentation and this mass had been gradually increasing in size. The patient had a febrile illness at the onset of his symptoms, which had now abated. There was no change in bowel habits. On examination, the clinician felt a firm mass in the right iliac fossa, which was also mildly tender and mobile.

The patient's blood counts were normal. Plain abdominal radiograph showed a curvilinear calcification in the right side of the pelvis (Fig. 1). An ultrasound examination showed a 6.2 cm x 3 cm cystic mass with internal echoes and a mural

nodule arising from its wall (Figs. 2a & 2b). Pre and post contrast CT scan showed that this was a well encapsulated ovoid mass, medial to the cecum and extending inferiorly, with curvilinear calcification in a portion of its wall (Fig. 3). The wall was noted to enhance after contrast administration. A mural enhancing nodule was also identified (Fig. 4). No enhancement of the cystic contents was noted.

A radiological diagnosis of mucocele of the appendix was made. At surgery, the diagnosis was confirmed and the appendix was carefully resected (Fig. 5). The cecum, terminal ileum and mesentery were noted to be normal, and no evidence of infection was noted. The histopathological diagnosis was mucocele of the appendix on top of mucinous cystadenoma with microscopy showing atypical proliferating mucous cells and papillary formation with some areas showing mucosal atrophy with fibrosis and inflammation.

DISCUSSION

Mucocele of the appendix are rare lesions representing 0.2 - 0.3% of surgical appendectomy specimens. They are pathologically divided into four categories. A very rare type is secondary to occlusion of the lumen from post-inflammatory scarring, age related atrophy, congenital obstruction of Gerlach's valve or extramural compression. This type leads to an atrophic mucosa. All other types are classified into a spectrum, from mucous hyperplasia to mucinous cystadenoma to mucinous cystadenocarcinoma,

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Fig. 1: Plain radiograph showing curvilinear calcification on the right side of the pelvis



Fig. 2a: Ultrasound showing cystic mass with internal echoes and calcification in its wall



Fig. 2b: Mural nodule in wall of cystic mass

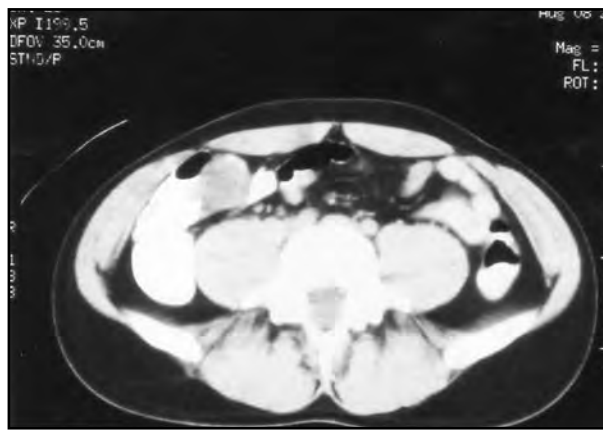


Fig. 3: Pre contrast CT showing discrete ovoid mass medial to the cecum with curvilinear calcification in its wall

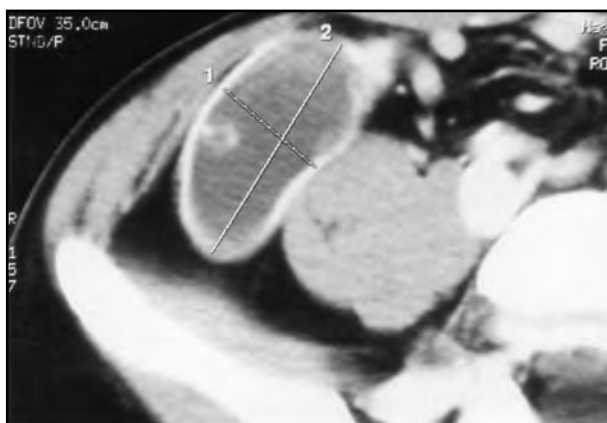


Fig. 4: Post contrast CT showing enhancing wall and mural nodule

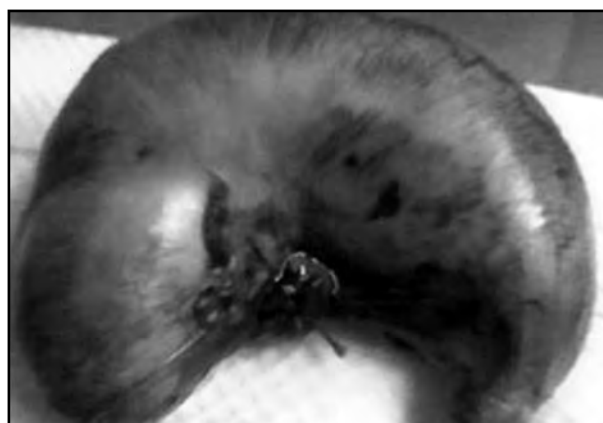


Fig. 5: Resected appendicular mucocoele

depending on the pathology of the mucosa. Whatever may be the cause, obstruction of the lumen and accumulation of yellow mucous within the appendiceal lumen results. About 25% of mucocoeles are from mucosal hyperplasia. These typically have minimal distension. Mucinous cystadenomas, which account for about 60% of mucocoeles, are more markedly distended. However, they are typically asymptomatic, and found incidentally. Mucocoeles up to 40 cm x 24 cm x 20 cm have been reported. About 20% have extra appendiceal

extrusion of mucus. If no cells are present in the peritoneal mucous, the prognosis is excellent. Mucinous cystadenocarcinomas, which constitute 10.15% of cases, are more likely symptomatic. This diagnosis is made by either neoplastic glands invading the wall or by the presence of cells in the peritoneal mucous. It is thought by some authors that pseudomyxoma peritonei is a complication of mucinous cystadenocarcinoma only.

Mucinous cystadenocarcinomas are extremely rare (benign: malignant about 10:1), but are

believed to arise in cystadenomas, and there is a high correlation of synchronous or metachronous colorectal adenomas and carcinomas (up to 20% in two series). There have also been reports of association with gastrointestinal tract, ovarian and kidney tumors. It is thought that only mucinous cystadenocarcinomas lead to pseudomyxoma peritonei^[1]. However, other authors believe this can complicate either benign or malignant mucoceles, although pseudomyxoma peritonei from the former would carry a better prognosis^[2-4]. A very important fact to be stressed here is the need for more mucoceles of the appendix to be diagnosed preoperatively. This makes the surgeon aware of the need for more careful surgery and consequently reduces the chances of iatrogenic damage to a mucocele with resultant leakage of the contents in the abdominal cavity with serious repercussions, especially pseudomyxoma peritonei^[1].

Onsonography, there is typically excellent through transmission and posterior wall enhancement. When the wall is calcified, posterior acoustic shadowing may occur, but often cannot be appreciated. The wall thickness varies, but if the wall is greater than 6 mm, one should also consider uncomplicated acute appendicitis. The internal features vary from anechoic to hyperechoic, and may be dependent. Internal septations, polypoid lesions extending into the lumen and irregular outline seem to be associated with the malignant variety, although some papillary processes may be seen in mucinous cystadenomas^[1,5,6]. The differential diagnosis on ultrasound include fluid filled small bowel, fluid in a small or large bowel diverticulum, appendiceal / diverticular abscess, mesenteric cyst seroma and particularly in females of reproductive age group, salpingitis and ectopic pregnancy masses^[5,7].

On CT, typically it is a low-attenuation (0 - 40 H.U.) smooth or lobulated mass. The more complex and irregularly shaped mucoceles tend to be mucinous cystadenocarcinomas. They may have single or multiple cystic components and some solid component. There may even be infiltration into adjacent organs such as the colon, ureter and bladder. Curvilinear or punctuate calcification in the lesion is

strongly suggestive of mucinous cystadenoma, and this is often not seen on plain films. Amorphous calcifications may be seen in the malignant type. This is from chronic inflammatory process incited by the irritating mucous. Vertical folds, mimicking intussusception, have also been described. A pitfall is that the fluid filled terminal ileum may resemble a mucocele, so delayed scanning may be warranted in some cases^[5,6].

The finding of an appendiceal mucocele should prompt a search for an associated tumor as there is six-fold increased incidence of colon adenocarcinoma and there may be association with mucin-secreting tumors of the ovary^[1].

CONCLUSION

Appendicular mucocele is to be considered in the differential diagnosis of a right iliac fossa mass and CT scan is imperative in the correct preoperative diagnosis. This helps the surgeon to be more careful and it reduces the risk of iatrogenic rupture of the mucocele with resultant leakage of its contents into the abdominal cavity causing pseudomyxoma peritonei^[7].

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

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Iodine Status among Pregnant Women in Kuwait

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Up to now, little has been known about iodine intake and the prevalence of iodine deficiency (ID), if any, in Kuwait. Urinary iodine excretion (UIE) and changes in thyroid function during pregnancy were thus evaluated.

Methods: Urinary iodide level was measured in random urine samples collected from 326 pregnant women at different gestational trimesters. Blood samples were drawn for free T4 (FT4) and TSH level determination.

Results: Median UIE levels fall within the normal range during all gestational trimesters i.e. >100 microg/l. However, if the new suggested recommendation for pregnant women <140 microg/l, is applied, median UIE values during trimesters 2 and 3 indicate ID. Mean serum TSH levels increased between trimesters 1 and 3 ($p<0.05$), whereas serum FT4 decreased between first and second trimesters ($p<0.05$), and this reduction continued at the third trimester. Furthermore, an increase in TSH levels for subjects with mild and moderate ID (Mi and Mo, respectively) were noticed ($p<0.05$) during the second trimester. However, FT4 levels dropped in subjects with Mi and Mo ID during the first trimester ($p<0.05$). In conclusion, these results suggest that 56.8% of pregnant women had median UIE level <145 microg/l, associated with high TSH and low FT4 levels.

Conclusion: Data obtained may indicate insufficient iodine intake among pregnant women in Kuwait.

Death Anxiety in Kuwaiti Middle-aged Personnel

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The present study aimed to examine the level of death anxiety, the sex-related differences among a middle-aged Kuwaiti personnel sample, and to explore the replicability of the Arabic Scale of Death Anxiety (ASDA) factors. A sample of 236 volunteer Kuwaiti personnel took part in the study. The mean ages of men and women were 41.5 (SD = 7.5) and 40.9 (SD = 7.1), respectively. The alpha reliability of the ASDA was found to be high (.93). Women had a significantly higher mean total score on the ASDA as well as on 17 out of its 20 items. Middle-aged personnel had a significantly lower mean ASDA total score than younger college students (M age = 22). The factor analysis of the ASDA items yielded three factors: fear of dead people and tombs; fear of postmortem events; and fear of lethal disease. These factors were highly replicable with previous factors extracted from a Kuwaiti college student sample. On the basis of the present findings, there are three general conclusions as follows: death anxiety is negatively associated with age; the sex-related differences on death anxiety are salient in the Arab samples; and the ASDA has a highly replicable factor structure.

Implications of Streptococcus Pneumoniae Penicillin Resistance and Serotype Distribution in Kuwait for Disease Treatment and Prevention

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Streptococcus pneumoniae causes serious infections. Treatment is difficult because of the emergence of penicillin resistance in *S. pneumoniae*. Pneumococcal vaccines offer the promise of control and prevention of pneumococcal infections. Serotype prevalence and penicillin susceptibility data for a country will predict the usefulness of the vaccines in that country. In Kuwait, the 23-valent polysaccharide and the 7-valent conjugate vaccines are being used without knowledge of the prevalent serotypes in the country. To obtain the necessary background information, data on penicillin susceptibility and serogroups were obtained from 397 consecutive clinical isolates collected during 2004 and 2005. Two hundred fifty-three isolates (64%) were penicillin resistant, and resistance was significantly higher in patients ≤ 15 years old and among the upper respiratory tract and eye isolates. The most common serotypes were 23F, 19F, 6A, 6B, 14, and 19A. Among the penicillin-resistant strains, the most common serotypes were 23F, 19F, 6B, 14, and 9A. Among the invasive strains, the most common serotypes were 14, 23F, 19A, and 9V. The polysaccharide vaccine gave 82% coverage against invasive infections in all age groups >2 years. The coverage of the 7-valent conjugate vaccine against invasive serotypes in children ≤ 2 years old was 55%. This moderate coverage by the conjugate vaccine against invasive infections in children necessitates a revised strategy on the use of the present conjugate vaccine and shows the need for formulation of an improved vaccine for superior coverage for Kuwait and possibly other countries of the Arabian Gulf.

Extended-spectrum Beta-lactamase-producing Escherichia Coli Isolated in the Al-Amiri Hospital in 2003 and Compared with Isolates from the Farwania Hospital Outbreak in 1994-96 in Kuwait

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J Chemother 2007; 19:271-276

Extended-spectrum beta-lactamases (ESBLs) are a major problem in Kuwait and an accurate method for their detection is essential. This study was designed to evaluate the efficacy of the commercial system (Vitek 2) to identify ESBLs in clinical isolates of *Escherichia coli* and relate this to their identification by agar dilution methods for use in a diagnostic laboratory. The presence of the major ESBLs parental enzyme groups was confirmed by PCR and the similarity of the strains was determined by pulsed field gel electrophoresis (PFGE) on DNA, cleaved using *Xba*I endonuclease, to identify clonal spread. Seventy-one separate *E. coli* isolates from 65 patients were tested. Sixty-two isolates were from 56 patients from the Al-Amiri Hospital and nine isolates from neonates from Farwania Hospital. The isolates were screened for ESBL activity by the Vitek 2 system. Isolates showing positive results were further tested with Etest ESBL strips and by the disc approximation methods. All the isolates were flagged as ESBL-positive by the Vitek 2 advanced expert system (AES). Isolates from all the 65 patients were detected as ESBL positive by the Etest, only if both ESBL strips were used. The double disc approximation test using five different antibiotics could detect ESBL presence in isolates from only 46 patients. In this test, the synergy with cefepime was the most sensitive in ESBL detection, showing their presence in 41 isolates. PCR with primers for *bla*(TEM) and *bla*(SHV) demonstrated that one or both of these enzymes in all isolates. PFGE revealed that many different clones were present amongst the isolates. The epidemiology of ESBL *E. coli* in Kuwait is complex. Many distinct strains are already present in the population, as shown by the results of PFGE. Several testing methods may be required to detect all strains harboring ESBLs.

Regional Analysis of the Ependyma of the Third Ventricle of Rat by Light and Electron Microscopy

Mathew TC

Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, Kuwait University, Kuwait

Anat Histol Embryol 2008; 37:9-18.

Ependymal lining of cerebral ventricles lies at the interface between the ventricular cavities and the brain parenchyma. Ependymal cells are involved in various functions within the brain and play a major role in the production of the chemical principals of the cerebrospinal fluid. Histological studies on the regional variation of the third ventricular ependyma and the subependyma of adult rats were carried out by light and electron microscopic methods. For light microscopic analysis, methacrylate sections were used. In addition to the routine haematoxylin and eosin (H and E) staining for histological studies, the sections were stained with toluidine blue, cresyl violet and periodic acid Schiff's reagent (PAS). A regional analysis of the ependyma of the third ventricle showed that in most regions the ependyma was monolayered. The sidewalls and floor of the ventral portion of the third ventricle showed a multilayered ependyma. For descriptive purposes at the light microscopic level, the ependymal cells were classified, based on the cell shape (flat, cuboidal or columnar), presence or absence of cilia and the number of cytoplasmic granules present in the cells. Studies of transmission electron microscope have shown that these granules represent the cell organelles of the ependyma. The subependyma also showed a regional morphological variation, and, in most instances, contained glial and neuronal elements. In regions of specific brain nuclei, neurons were the major cell type of the subependyma. PAS staining did not show any positive granules in the ependymal cytosol. Characteristic supraependymal elements were present at the ependymal surface of the third ventricle.

Emergence of Multidrug-Resistant Salmonella Spp. and Isolates with Reduced Susceptibility to Ciprofloxacin in Kuwait and the United Arab Emirates

Rotimi VO, Jamal W, Pal T, Sonnevend A, Dimitrov TS, Albert MJ

Department of Microbiology, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat 13110, Kuwait

Diagn Microbiol Infect Dis 2008; 60:71-77

Kuwait and United Arab Emirates (UAE) are 2 countries with worldwide significance in the context of global epidemiology of antimicrobial resistance. The extent of drug resistance in *Salmonella* spp. isolated from these countries was investigated by determining their susceptibility to 9 antibiotics using the E-test method. Amikacin, cefotaxime, ceftriaxone, ciprofloxacin, and gentamicin had excellent activities against all Kuwait and UAE isolates with MIC(90)s ranging between 0.056 and 4.5 µg/mL. The resistance rates in Kuwait and UAE to ampicillin were 26.5% and 17.1%, cefotaxime/ceftriaxone 1.6% and 1.6%, ciprofloxacin 1.2% and 0.8%, chloramphenicol 5.6% and 5.7%, and trimethoprim-sulfamethoxazole 26.1% and 8.9%, respectively. A total of 9.8% of the Kuwait isolates were multidrug resistant versus 4.1% of UAE isolates. Reduced susceptibility to ciprofloxacin was observed in 14.2% and 7.4% of the nontyphoidal *Salmonella*, respectively, as were in 44% of *Salmonella enterica* serovar typhi and 66.7% *Salmonella paratyphi*. *Salmonella* spp. with reduced quinolones susceptibility have emerged in the Gulf region, and this is of concern as it may compromise the treatment of infections caused by invasive strains

Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2008, 40 (1): 84-88

Internal Medicine: Current Clinical Topics for the Primary Care Setting

Mar 01-31, 2008

Sarasota, FL, *United States*

Contact: Eva or Cristina

Tel: 1-866-267-4263 (toll free), 1-941-388-1766; Fax: 1-941-365-7073

E-Mail: mail@ams4cme.com

Perioperative Management

Mar 02-05, 2008

Marco Island, FL, *United States*

Contact: Office of Continuing Medical Education

Tel: 410-955-2959; Fax: 410-955-0807

E-Mail: cmenet@jhmi.edu

The 14th World Congress of **Anaesthesiologists**

Mar 02-07, 2008

Cape Town, *South Africa*

Contact: Barbara Quantz

Tel: 00-32-26-417-470; Fax: 00-32-26-417-471

E-Mail: Info@optionsglobal.com

Infectious Diseases: Adult Issues in the Outpatient and Inpatient Settings

Mar 04-10, 2008

Sarasota, FL, *United States*

Contact: Eva or Cristina

Tel: 1-866-267-4263 (toll free), 1-941-388-1766; Fax: 1-941-365-7073

E-Mail: mail@ams4cme.com

2nd International Conference on **Hypertension, Lipids, Diabetes and Stroke Prevention**

Mar 06-08, 2008

Prague, *Czech Republic*

Contact: Jo Jackson

Tel: 41-229-080-488; Fax: 41-227-322-850

E-Mail: strokeprevention08@kenes.com

Society of **Cardiovascular Anesthesiologists** 13th

Annual Update on Cardiopulmonary Bypass

Mar 09-15, 2008

Whistler, BC, *Canada*

Contact: SCA

Tel: 804-282-0084; Fax: 804-282-0090

E-Mail: sca@societyhq.com

Cardiovascular Risk Reduction and Mature Women's Health

Mar 10-20, 2008

New York, NY, *United States*

Contact: Cindy Smyth

Tel: 1-877-536-6736

E-Mail: vacations@kennedyseminars.com

STD Intensive

Mar 11-13, 2008

Denver, CO, *United States*

Contact: CME Office

Tel: 1-800-207-9399 / 513-558-7277; Fax: 513-558-1708/513-558-1756

E-Mail: uccme@uc.edu

1st Iberican Congress of **Internal Medicine**

Mar 12-15, 2008

Vilamoura, *Portugal*

Contact: Meeting Organiser

Tel: 351-217-520-570; Fax: 351-217-520-579

E-Mail: secretariado@spmi.webside.pt

Total **Endovascular Series** Lower Extremity 1 Symposium

Mar 13-15, 2008

Houston, TX, *United States*

Contact: Kristen Brought

Tel: 713-965-0566; Fax: 713-960-0488

E-Mail: tes@meetingmanangers.com

16th Annual Meeting of The Asian Society for **Cardiovascular Surgery**

Mar 13-16, 2008

Singapore, *Singapore*

Contact: Kelly Chan

Tel: 63-464-402; Fax: 63-464-403

E-Mail: mice@themeetinglab.com

24th Annual **Cardiovascular** Conference

Mar 16-20, 2008

Lake Louise, AB, *Canada*

Contact: Dr. Peter Klinke

Tel: 1-877-595-1884 (toll free); Fax: 250-595-5367

E-Mail: peterklinke@vhif.org

Family Medicine: An Evidence-Based Approach to Patient Care

Mar 17-21, 2008

Sarasota, FL, *United States*

Contact: Eva or Cristina

Tel: 1-866-267-4263 (toll free), 1-941-388-1766; Fax: 1-941-365-7073

E-Mail: mail@ams4cme.com

STD Intensive

Mar 17-21, 2008

Cincinnati, OH, *United States*

Contact: CME Office

Tel: 1-800-207-9399 / 513-558-7277; Fax: 513-558-1708/513-558-1756

E-Mail: uccme@uc.edu

The 6th Annual Scientific Conference of Saudi Thoracic Society

Mar 18-20, 2008

Riyadh, *Saudi Arabia*

Contact: Professor Mohamed Al-Hajjaj

Tel: 00-96-612-488-966; Fax: 00-96-612-487-431

E-Mail: saudithoracicsociety@gmail.com

28th International Symposium on Intensive Care and Emergency Medicine

Mar 18-21, 2008

Brussels, *Belgium*

Contact: Natercia Tavares

Tel: 32-25-553-631; Fax: 32-25-554-555

E-Mail: nta@intensive.org

10th KFAFH International Cardiac Symposium 2008

Mar 19-20, 2008

Jeddah, *Saudi Arabia*

Contact: Dr. Mai N. Al Barakati

Tel: 96-626-651-868 ext 30-68; Fax: 96-626-651-868

E-Mail: cardiac@kfahf.med.s

Breast Imaging Update

Mar 21-23, 2008

San Francisco, CA, *United States*

Contact: UCSF Office of Continuing Medical Education, 3333 California Street, Room 450, San Francisco, CA 9411

Tel: 415-476-4251 / 415-476-5808; Fax: 415-476-0318 / 415-502-1795

E-Mail: info@ocme.ucsf.edu

Internal Medicine: A Clinical Update

Mar 24-28, 2008

Sarasota, FL, *United States*

Contact: Eva or Cristina

Tel: 1-866-267-4263 (toll free), 1-941-388-1766; Fax: 1-941-365-7073

E-Mail: mail@ams4cme.com

The 2nd Scientific Symposium of Al-Wali Hospital-Anorectal Diseases Today and Tomorrow

Mar 25-27, 2008

Aden, *Yemen*

Contact: Dr Abdulhakim Al-Tamimi

Tel: 00-967-733-422-323; Fax: 00-96-72-395-353

E-Mail: abotammam11@yahoo.com

12th Pan Arab Conference on Diabetes PACD12

Mar 25-28, 2008

Cairo, *Egypt*

Contact: Mahmoud Ibrahim, MD

Tel: 2-0-122-131-868; Fax: 2-0-22-723-693

E-Mail: mahmoud@arab-diabetes.com

Clinical Trials: ICH GCP meeting

Mar 27-29, 2008

Kiev, *Ukraine*

Contact: Kristina Shevchenko

E-Mail: dr@nbscience.com

Cardiac Surgery Update and Progress - CSUP

Mar 29-Apr 05, 2008

Lech-Zürs, *Austria*

Contact: E&E PCO

Tel: 43-18-674-944-0; Fax: 43-18-674-944-9

E-Mail: office@ee-pco.com

3rd British Society of Cardiovascular Magnetic Resonance Meeting

Apr 02, 2008

Leeds, England, *United Kingdom*

Contact: Michelle Glanville

Tel: 44-1-865-391-215

E-Mail: Info@bscmr.org

22nd European Immunogenetics and Histocompatibility Conference

Apr 02-05, 2008

Toulouse, *France*

Contact: Mogens Thomsen

Tel: 33-561-322-06; Fax: 33-561-322-084

E-Mail: thomsen@toulouse.inserm.fr

Australasian Society for Infectious Diseases Annual Scientific Meeting

Apr 02-05, 2008

Cooloom, QLD, *Australia*

Contact: Daliah Frank

Tel: 61-282-040-770; Fax: 61-292-124-670

E-Mail: conferenceinfo@ashm.org.au

Reproductive Endocrinology and Infertility

Apr 03-04, 2008

San Francisco, CA, *United States*

Contact: UCSF Office of Continuing Medical Education, 3333 California Street, Room 450, San Francisco, CA 9411

Tel: 415-476-4251 / 415-476-5808; Fax: 415-476-0318 / 415-502-1795

E-Mail: info@ocme.ucsf.edu

The Houston Aortic Symposium: Frontiers in Cardiovascular Diseases

Apr 04-06, 2008

Houston, TX, *United States*

Contact: Cindy Brown

Tel: 760-720-2263; Fax: 760-720-6263

E-Mail: cbrown@promedicacme.com

Celebration of Pediatric Pulmonology 2008

Apr 04-06, 2008

Fort Lauderdale, FL, *United States*

Contact: ACCP Customer Relations

Tel: 847-498-1400; Fax: 847-498-5460

E-Mail: jjohnston@chestnet.org

New Horizons in Anesthesiology

Apr 06-11, 2008

Cozumel, *Mexico*

Contact: Office of Continuing Medical Education

Tel: 404-727-5695; Fax: 404-727-5667

E-Mail: cme@emory.edu

Dubai International Emergency & Catastrophe Management Conference

Apr 08-10, 2008

Dubai, *United Arab Emirates*

Contact: DR.Firas Annajjar

Tel: 00-971-503-534-422

E-Mail: fjknajjar@yahoo.com

1st International Congress on Prehypertension & Cardiometabolic Risk

Apr 09-12, 2008

Prague, *Czech Republic*

Contact: Jo Jackson

Tel: 41-229-080-488; Fax: 41-227-322-850

E-Mail: prehypertension@kenes.com

CARDIO ATHENA 2008 - International Meeting on Cardiovascular Medicine

Apr 11-12, 2008

Athens, *Greece*

Contact: Mrs. Penelope Mitroyianni

Tel: 302-107-257-693; Fax: 302-107-257-532

E-Mail: Info@erasmus.gr

Molecular Biology in Cardiovascular Medicine

Apr 14-17, 2008

England, *United Kingdom*

Contact: Dr Charlotte Moonan

Tel: 0-24-76-523-540; Fax: 0-24-76-523-701

E-Mail: Charlotte.Moonan@warwick.ac.uk

7th Cardiology Update 2008

Apr 17-19, 2008

Athens, *Greece*

Contact: Lilian Sait

Tel: 00-302-107-753-180; Fax: 00-302-107-753-101

E-Mail: lsait@ath.forthnet.gr

Evivenice 2008 - Venice Course on Extreme Vascular Interventions

Apr 17-19, 2008

Venice, *Italy*

Contact: OSC Healthcare

Tel: 00-39-0-51-224-232; Fax: 00-39-0-51-226-855

E-Mail: info@evivenice.com

Immunopharmacology 2008

Apr 19-22, 2008

Varadero Beach, *Cuba*

Contact: Dr. Gabino Garrido

Tel: 00-5-372-725-222; Fax: 00-5-372-736-471

E-Mail: gabino.garrido@infomed.sld.cu

9th International Conference of the Jordan Cardiac Society

Apr 22-25, 2008

Amman, *Jordan*

Contact: Mohannad Ramini

Tel: 00-96-265-539-771; Fax: 00-96-265-510-090

E-Mail: araborganizers@index.com.jo

5th Annual Team Echocardiography: The Heart of Cardiovascular Medicine

Apr 24-27, 2008

Hilton Head Island, *United States*

Contact: Louise Nixon

Tel: 336-716-4505; Fax: 336-716-2447

E-Mail: cmu@wfubmc.edu

HIV Management 2008: The New York Course

Apr 25-26, 2008

New York NY, *United States*

Contact: Executive Director

Tel: 888-391-3996; Fax: 508-528-7880

E-Mail: info@newyorkcourse.com

Clinical Trials: ICH GCP meeting

Apr 27-28, 2008

Kiev, *United States*

Contact: Kristina Shevchenko

E-Mail: dr@nbscience.com

The Pharmaceutical and Biotechnology Middle East (PABME) exhibition and conference
Apr 27-29, 2008
Dubai International Exhibition Centre, *UAE*
Organizer: IIR Middle East
Contact: www.pabme.com
Tel: +971 4 3365161; Fax +971 4 3364021

10th Congress of the European Society of Contraception. Non-contraceptive impact of Contraception and Family Planning
Apr 30-May 03, 2008
Prague, *Czech Republic*
Contact: ESC Central Office
Tel: 32-25-820-852; Fax: 32-25-825-515
E-Mail: esccentraloffice@contraception-esc.com

40th Annual Meeting of the Society for Obstetric Anesthesia and Perinatology
Apr 30-May 04, 2008
Chicago, IL, *United States*
Contact: SOAP Headquarters
Tel: 216-447-7863; Fax: 216-642-1127
E-Mail: soaphq@soap.org

Cardiology, Pulmonary and Critical Care Medicine: A Collection of the Most Useful Topics
May 01-31, 2008
Sarasota, FL, *United States*
Contact: Eva or Cristina
Tel: 1-866-267-4263 (toll free), 1-941-388-1766; Fax: 1-941-365-7073
E-Mail: mail@ams4cme.com

3rd International Romanian Congress of Anti-Aging Medicine
May 02-04, 2008
Bucharest, *Romania*
Contact: Catalin Enachescu
Tel: 40-723-034-834, Fax: 40-214-130-212
E-mail: congress@theantiaging.ro

General Medical Topics CME Cruise
May 04-17, 2008
Johannesburg, *South Africa*
Contact: Dr. Martin Gerretsen
Tel: 1-888-647-7327; Fax: 1-888-547-7337
E-Mail: cruises@seacourses.com

Update in Internal Medicine
May 07-09, 2008
Rootstown, OH, *United States*
Contact: Mary Sherman
Tel: 330-325-6575
E-Mail: mas@neoucom.edu

Disease Management Conference 2008
May 08-10, 2008
Singapore, *Singapore*
Contact: Pam Wong
Tel: 65-64-966-850; Fax: 65-64-966-853
E-Mail: conferenceinfo@nhg.com.sg

1st International Online Medical Conference (IOMC 2008)
May 10-11, 2008
Tehran, *Iran*
Contact: Mostafa Nejati
Tel: 00-989-124-265-604
E-Mail: iomc@ala.ir

Cytokines 2008
May 10-15, 2008
Kololi, *Gambia*
Contact: Anthony F. England, Ph.D.
Tel: +31 30 214 5715
E-Mail: england@mangosee.com

The 6th International Workshop on Drug Delivery Systems for Nanomedicine: Nanostructures and their Biomedical Applications
May 13-16, 2008
Trest, *Czech Republic*
Contact: Monika Fialová
Tel: 42-0-261-174-305; Fax: 42-0-261-174-307
E-Mail: monika.fialova@czech-in.cz

Obstetric Anaesthesia 2008
May 14-16, 2008
Belfast, *Ireland*
Contact: Meeting Secretariat
Tel: 44-2-087-411-311; Fax: 44-2-087-410-611
E-Mail: www.oaameetings.info

Seminar on Legal-Medical Issues
May 16-31, 2008 3
Fort Lauderdale, FL, *United States*
Contact: Eileen Tener
Tel: 813-333-6878
E-Mail: etener@cruiseplanners.com

XVI World Congress of Cardiology
May 18-21, 2008
Buenos Aires, *Argentina*
Contact: Meeting Organiser
E-Mail: congress@worldheart.org

Cardiology Essentials and Case Studies
May 21-Jun 02, 2008
Civitavecchia, *Italy*
Contact: Eileen Tener
Tel: 813-333-6878
E-Mail: etener@CruisersParadise.com

Cardiovascular CT at Concord

May 23-25, 2008

Sydney, NSW, *Australia*

Contact: Tara Montgomery

Tel: 61-295-187-722

E-Mail: info@CCTatConcord.com

1st International Congress of Translational Oncology

May 24-25, 2008

Kastro Kyllinis, *Greece*

Contact: Dr John Giannios

Tel: 69-74-711-158

E-Mail: jng@otenet.gr

18th Annual Anatomic Pathology Updated Course

May 24-29, 2008

Bethesda, MD, *United States*

Contact: Ricky Giles

Tel: 202-782-2637; Fax: 202-782-5020

E-Mail: came@afip.osd.mil

IV International Symposium of Hypertension HTA 2008 and II International WorkShop of Vascular Risk

May 26-29, 2008

Santa Clara, *Cuba*

Contact: Emilio F. González, MD., PhD.

Tel: 53-42-281-351; Fax: 53-42-281-449

E-Mail: hta2008@uclv.edu.cu

The 2nd Asia-Pacific Congress of Pediatric Cardiology and Cardiac Surgery

May 27-30, 2008

Jeju Island, *Republic of Korea*

Contact: Song Yi KIM

Tel: 82-3452-7291; Fax: 82-3452-7292

E-Mail: pccs2008@intercom.co.kr

Clinical Trials: ICH GCP meeting

May 28-29, 2008

Kiev, *Ukraine*

Contact: Kristina Shevchenko

E-Mail: dr@nbscience.com

Emergency Medicine: An Evidence-Based Approach for Improving Outcomes

Jun 01-30, 2008

Sarasota, FL, *United States*

Contact: Eva or Cristina

Tel: 1-866-267-4263 (toll free), 1-941-388-1766; Fax: 1-941-365-7073

E-Mail: mail@ams4cme.com

DVD - Dermatology: Recognition and Management for Primary Care, Volume III

Jun 01-30, 2008

Sarasota, FL, *United States*

Contact: Eva or Cristina

Tel: 1-866-267-4263 (toll free), 1-941-388-1766; Fax: 1-941-365-7073

E-Mail: mail@ams4cme.com

43rd Congress of the Polish Society of Otolaryngologists

Jun 04-07, 2008

Lodz, *Poland*

Contact: Marcin Durko M.D

Tel: 48-426-785-785; Fax: 48-426-785-785

E-Mail: sekretariat@orl2008.pl

The 1st International Congress of Infection in Transplantation and Cancer

Jun 10-12, 2008

Tehran, *Iran*

Contact: Meeting Organiser

Tel: 00-982-122-424-205-10; Fax: 00-982-122-424-206

E-Mail: info@idtmrc.ac.ir

Food as Medicine

Jun 12-15, 2008

Baltimore, MD, *United States*

Contact: Klara Royal

Tel: 202-966-7338 ext 241; Fax: 202-966-2589

E-Mail: fam@cmbm.org

Heart Failure 2008 Congress

Jun 14-17, 2008

Milan, *Italy*

Contact: Sabrina Volle

Tel: 33-0-492-947-600; Fax: 33-0-492-947-601

E-Mail: HFsecretariat@escardio.org

Infectious Disease Update

Jun 16-27, 2008

Harwich, England, *United Kingdom*

Contact: Eileen Tener

Tel: 813-333-6878

E-Mail: etener@CruisersParadise.com

CARDIOSTIM - 16th world congress in Cardiac Electrophysiology and Cardiac Techniques

Jun 18-21, 2008

Nice, *France*

Contact: Clarisse Sable

Tel: 33-147-565-084; Fax: 33-147-562-466

E-Mail: cardiostim@reedexpo.fr

WHO-Facts Sheet

1. Child-Specific Medicines, A Global Priority
2. Global HIV Prevalence has Levelled Off
3. Status of Global Efforts Against Tobacco and WHO's Policy Package
4. Home Treatment for Children with Severe Pneumonia Just as Effective as Hospital

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2008, 40 (1): 89-94

1. CHILD-SPECIFIC MEDICINES, A GLOBAL PRIORITY

Reducing child mortality and treating children affected by major diseases are global priorities expressed in the Millennium Development Goals (Goals Four and Six <http://www.un.org/millenniumgoals>). A pre-condition to achieve these goals is increased production and availability of essential medicines for children. At present, many medicines for priority diseases are not developed for children; and when they are, they are not reaching the children who need them most.

Children metabolize medicines differently from adults. They therefore need different dosage forms. Differences also exist between children of different ages, body weight and physical conditions. Child-specific medicines are those manufactured to suit the age, physical condition and body weight of the child taking them.

Apart from dosage, child specific medicines need to be in a format that is palatable to children. Small children have trouble swallowing big tablets but can tolerate oral solution or syrups. For children with chronic conditions such as HIV/AIDS, where several medicines must be taken daily, the fixed-dose combination approach - several medicines in one pill - is best. However, the few existing paediatric fixed dose combinations developed for children are generally three times more expensive than the adult dosage form.

Research and development gaps

There is little knowledge about the effects certain medicines can have on children. This is partly due to the fact that fewer clinical trials are conducted in children than in adults. The ethical approach

to conducting clinical trials is to obtain signed informed consent from volunteers before they take part in a trial. Obtaining informed consent from a child - particularly in the younger age bracket - is clearly difficult. Insufficient clinical trials for paediatric medicines in turn lead to information gaps related to quality and safety. Those gaps deter pharmaceutical companies from researching and developing child-friendly medicines and generics companies from producing them at lower cost.

In addition, children are generally a silent sector of the population, relying on others to speak for them - they do not vote, they do not buy and generally do not have a public voice in society. Although they would benefit from more pharmaceutical research and development, they do not have the means to demand it.

Distribution problems

Child specific medicines already developed and available, often do not reach the children who need them most. For instance, diarrhoea, which can easily be treated with oral rehydration salts plus zinc, still kills 1.9 million under-fives every year. Oral rehydration salts are easy to use, easy to manufacture and relatively inexpensive. Due to years of advocacy campaigns, they are widely available in developing countries. Zinc, on the other hand, is not easily found in areas with a high incidence of diarrhoeal disease. Oral rehydration solution with zinc is more effective than without it. There may be numerous, poverty-related causes for the fact that children are still dying of diarrhoeal diseases, but one obvious reason is that the full remedy - rehydration salts plus zinc - is not made available to them.

Address correspondence to:

Office of the Spokesperson, WHO, Geneva. Tel.: (+41 22) 791 2599; Fax (+41 22) 791 4858; E-mail: inf@who.int; Web site: <http://www.who.int/>

The target diseases

WHO estimates that of all the child killers, five conditions in particular demand immediate action:

- **Pneumonia and other acute lower respiratory infections**

An estimated 20% of all deaths in children under-five are due to acute lower respiratory infections, representing the single most important cause of infant mortality worldwide. Pneumonia alone causes approximately 2 million deaths every year which could be prevented with proper access to child-specific medicines.

- **HIV/AIDS**

Although contributing to only about 3% of all annual deaths in children under-five, paediatric HIV is a growing public health challenge. Every day, an estimated 1150 children become infected.

- **Malaria**

An estimated 1 million children die every year due to malaria infection and 40% of the world's children live in malaria-endemic countries. In Africa, a child dies of malaria every 30 seconds. Although malaria is a priority illness and has been the subject of numerous global conferences and calls to action, the issues of access to and development of child specific treatment need to be further addressed.

- **Diarrhoeal diseases**

An estimated 1.9 million children under five die each year from diarrhoea and related complications. This amounts to 18% of all under-five deaths and means that more than 5000 children die every day as a result of diarrhoeal diseases, which can be treated easily and effectively.

- **Tuberculosis**

About 1.1 million (12%) of the 8.8 million new tuberculosis cases in 2005 occurred in children under 14 years of age.

Lymphatic filariasis and schistosomiasis

Although not major killers of children, the neglected tropical diseases filariasis and schistosomiasis are also prioritized by WHO because of gaps in either the development or accessibility of medicines. WHO estimates that 330 million children under 15 years of age currently require chemotherapy to prevent Lymphatic Filariasis in endemic areas (Asia, Pacific, Africa and South America). Another 125 million children in the same age category require preventive treatment for

schistosomiasis. The necessary medicines exist in paediatric form but are hardly available or accessible to the targeted populations.

WHO action

Recognizing the lack of child specific medicines, the Member States of WHO passed a resolution on "Better Medicines for Children" during the 2007 World Health Assembly, the Organization's annual meeting.

In order to explore ways to promote more research and development into paediatric medicines and to improve knowledge on the quality, effectiveness and safety of these medicines, WHO created an Expert Sub-Committee to develop an essential medicines list for children. The list, finalized and published in December 2007, consists of 206 medicines, including anti-AIDS treatment, vaccines, anaesthetics, hormones, vitamins and minerals.

The list should serve as a reference for countries to develop national lists according to their specific public health priorities, and is the beginning of a longer process to ensure that child specific medicines are developed and delivered to the intended patient group.

The initial objective of WHO's work in this area is to tackle HIV/AIDS, malaria, tuberculosis, pneumonia and diarrhoeal diseases, which account for over 50% of under-five mortality.

More specifically, WHO will work towards the following objectives:

- Increase additional and independent studies on the development of paediatric medicines and their efficacy and safety;
- Provide better information on child specific medicines to prescribers, pharmacists and health workers;
- Explore ways of fast-tracking the regulation of quality paediatric formulations;
- Establish systems for ensuring that health facilities have adequate stocks of essential medicines and clinical consumables for children;
- In the absence of clinical trials, identify safety and efficacy indications for which essential medicines may be used in paediatric formulations;
- Improve infrastructure and equipment to store liquid paediatric formulations which are less stable than solid dosages;
- Monitor the use of unlicensed, off-label and unsafe medicines for children.

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2. GLOBAL HIV PREVALENCE HAS LEVELLED OFF

Improvements in surveillance increase understanding of the epidemic, resulting in substantial revisions to estimates

New data show global HIV prevalence—the percentage of people living with HIV—has levelled off and that the number of new infections has fallen, in part as a result of the impact of HIV programmes. However, in 2007 33.2 million [30.6 – 36.1 million] people were estimated to be living with HIV, 2.5 million [1.8 – 4.1 million] people became newly infected and 2.1 million [1.9 – 2.4 million] people died of AIDS.

There were an estimated 1.7 million [1.4 – 2.4 million] new HIV infections in sub-Saharan Africa in 2007 - a significant reduction since 2001. However, the region remains most severely affected. An estimated 22.5 million [20.9 – 24.3 million] people living with HIV, or 68% of the global total, are in sub-Saharan Africa. Eight countries in this region now account for almost one-third of all new HIV infections and AIDS deaths globally.

Since 2001, when the United Nations Declaration of Commitment on HIV/AIDS was signed, the number of people living with HIV in Eastern Europe and Central Asia has increased by more than 150% from 630 000 [490 000 – 1.1 million] to 1.6 million [1.2 – 2.1 million] in 2007. In Asia, the estimated number of people living with HIV in Viet Nam has more than doubled between 2000 and 2005 and Indonesia has the fastest growing epidemic.

These findings were released today by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) in the report '2007 AIDS Epidemic Update'.

Continuing improvements to latest estimates

The new report reflects improved and expanded epidemiological data and analyses that present a better understanding of the global epidemic. These new data and advances in methodology have resulted in substantial revisions from previous estimates.

While the global prevalence of HIV infection—the percentage of people infected with HIV - has levelled off, the total number of people living with HIV is increasing because of ongoing acquisition of HIV infection, combined with longer survival times, in a continuously growing general population.

Global HIV incidence - the number of new HIV infections per year - is now estimated to have peaked in the late 1990s at over 3 million [2.4 – 5.1 million] new infections per year, and is estimated in 2007 to be 2.5 million [1.8 – 4.1 million] new infections, an average of more than 6 800 new infections each day.

This reflects natural trends in the epidemic, as well as the result of HIV prevention efforts.

The number of people dying from AIDS-related illnesses has declined in the last two years, due in part to the life prolonging effects of antiretroviral therapy. AIDS is among the leading causes of death globally and remains the primary cause of death in Africa.

"These improved data present us with a clearer picture of the AIDS epidemic, one that reveals both challenges and opportunities," said UNAIDS Executive Director Dr Peter Piot. "Unquestionably, we are beginning to see a return on investment—new HIV infections and mortality are declining and the prevalence of HIV levelling. But with more than 6 800 new infections and over 5 700 deaths each day due to AIDS we must expand our efforts in order to significantly reduce the impact of AIDS worldwide."

Revision of estimates

UNAIDS, WHO and the Reference Group on Estimates, Modelling and Projections have recently undertaken the most comprehensive review of their methodologies and monitoring systems since 2001. The epidemic estimates presented in this year's report reflect improvements in country data collection and analysis, as well as a better understanding of the natural history and distribution of HIV infection. This information is vital in helping countries understand their epidemics and respond to them more effectively.

UNAIDS and WHO are now working with better information from many more countries. In the past few years a number of countries, most notably in sub-Saharan Africa and Asia, have expanded and improved their HIV surveillance systems, conducting new, more accurate studies that provide more precise information about HIV prevalence than earlier studies. In addition, 30 countries mostly in Africa have conducted national representative population-based household surveys. These have also informed adjustments for other countries with similar epidemics that have not conducted these surveys. New assumptions have also been made as a result of a better understanding of the natural history of untreated HIV infection.

The current estimate of 33.2 million [30.6 – 36.1 million] people living with HIV replaces the 2006 estimate of 39.5 million [24.5 – 47.1 million]. Applying the improved methodology retrospectively to the 2006 data, the 2007 report revises that figure, now estimating that in 2006 there were 32.7 million [30.2 – 35.3 million] people living with HIV. The single biggest reason for the reduction in global HIV prevalence figures in the past year was the recent revision of estimates in India after an intensive

reassessment of the epidemic in that country. The revised estimates for India, combined with important revisions of estimates in five sub-Saharan African countries (Angola, Kenya, Mozambique, Nigeria, and Zimbabwe) account for 70% of the reduction in HIV prevalence as compared to 2006 estimates.

"Reliable public health data are the essential foundation for an effective response to HIV/AIDS", said WHO's HIV/AIDS Director Dr Kevin De Cock. "While these new estimates are of better quality than those of the past, we need to continue investing more in all countries and all aspects of strategic information relating to health."

"The data for measuring the HIV epidemic used by UNAIDS/WHO has considerably expanded and improved in recent years," said Ron Brookmeyer, Professor of Biostatistics and Chair of the Master of Public Health Program, The Johns Hopkins Bloomberg School of Public Health. "Nevertheless, there is a need to further improve the representativeness of the underlying data. There is a need to expand disease surveillance systems to better track the sub-epidemics in risk populations within each country."

"More accurate estimates and trends will ultimately lead to improvements in the design and evaluation of prevention programmes," added Professor Brookmeyer, who was also the Chair of the Independent Review Panel at the recent International Consultation on epidemiological estimates convened by UNAIDS and WHO. UNAIDS and WHO will continue to update their methodology as new data becomes available from research studies and surveillance data from countries.

Progress seen but more needs to be done

HIV prevalence among young pregnant women (15 – 24), attending antenatal clinics, has declined since 2000/2001 in 11 of the 15 most-affected countries. Preliminary data also show favorable changes in risk behavior among young people in a number of countries (Botswana, Cameroon, Chad, Haiti, Kenya, Malawi, Togo, Zambia, and Zimbabwe). These trends suggest that prevention efforts are having an impact in several of the most affected countries.

In sub-Saharan Africa, continued treatment scale-up and HIV prevention efforts are also bringing results in some countries, but mortality from AIDS remains high in Africa due to the extensive unmet treatment need. Cote d'Ivoire, Kenya and Zimbabwe, among others, have all seen downward trends in their national prevalence. Beyond sub-Saharan Africa, declines in new HIV infections have also occurred in South and South-East Asia, notably in Cambodia, Myanmar and Thailand.

There is a need to adapt and revive HIV prevention efforts as some countries are seeing a reversal of declining trends. Burundi's declining trend from the late 1990's did not continue beyond 2005 and HIV prevalence started to increase again at most surveillance sites. Despite achievements in reversing the epidemic in Thailand, HIV prevalence is rising among men who have sex with men and has remained high among injecting drug users over the past 15 years, ranging between 30% to 50%.

UNAIDS and WHO officials point out that the new estimates do not change the need for immediate action and increased funding to scale up towards universal access to HIV prevention, treatment, care and support services.

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3. STATUS OF GLOBAL EFFORTS AGAINST TOBACCO AND WHO'S POLICY PACKAGE

The World Health Organization (WHO) released new data showing that while progress has been made, not a single country fully implements all key tobacco control measures, and outlined an approach that governments can adopt to prevent tens of millions of premature deaths by the middle of this century.

In a new report presenting the first comprehensive analysis of global tobacco use and control efforts, WHO expressed that only 5% of the world's population live in countries that fully protect their population with any one of the key measures that reduce smoking rates. The report also revealed that governments around the world collect 500 times more money in tobacco taxes each year than they spend on anti-tobacco efforts. It finds that tobacco taxes, the single most effective strategy, could be significantly increased in nearly all countries, providing a source of sustainable funding to implement and enforce the recommended approach, a package of six policies called MPOWER as below:

- Monitor tobacco use and prevention policies
- Protect people from tobacco smoke
- Offer help to quit tobacco use
- Warn about the dangers of tobacco
- Enforce bans on tobacco advertising, promotion and sponsorship
- Raise taxes on tobacco

"While efforts to combat tobacco are gaining momentum, virtually every country needs to do more. These six strategies are within the reach of

every country, rich or poor and, when combined as a package, they offer us the best chance of reversing this growing epidemic," said Dr Margaret Chan, Director-General of WHO. Dr Chan launched the WHO Report of the Global Tobacco Epidemic at a news conference with New York Mayor Michael Bloomberg who remarked that "No country fully implements all of the MPOWER policies and 80% of countries don't fully implement even one policy. While tobacco control measures are sometimes controversial, they save lives and governments need to step up and do the right thing."

The report also documents the epidemic's shift to the developing world, where 80% of the more than eight million annual tobacco-related deaths projected by 2030 are expected to occur.

This shift, the report says, results from a global tobacco industry strategy to target young people and adults in the developing world, ensuring that millions of people become fatally addicted every year. The targeting of young women in particular is highlighted as one of the "most ominous potential developments of the epidemic's growth."

WHO is also working with global partners to scale-up the help that can be offered to countries to implement the strategies. Dr Douglas Bettcher, Director of WHO's Tobacco Free Initiative, said the six MPOWER strategies would create a powerful response to the tobacco epidemic. "This package will create an enabling environment to help current tobacco users quit, protect people from second-hand smoke and prevent young people from taking up the habit," he said.

Other key findings in the report include:

- Only 5% of the global population is protected by comprehensive national smoke-free legislation and 40% of countries still allow smoking in hospitals and schools;
- Only 5% of the world's population lives in countries with comprehensive national bans on tobacco advertising and promotion;
- Just 15 countries, representing 6% of the global population, mandate pictorial warnings on tobacco packaging;
- Services to treat tobacco dependence are fully available in only nine countries, covering 5% of the world's people;
- Tobacco tax revenues are more than 4000 times greater than spending on tobacco control in middle-income countries and more than 9000 times greater in lower-income countries. High-income countries collect about 340 times more money in tobacco taxes than they spend on tobacco control.

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4. HOME TREATMENT FOR CHILDREN WITH SEVERE PNEUMONIA JUST AS EFFECTIVE AS HOSPITAL

Pneumonia is the largest single killer of children under five years old around the world. Almost four children die from pneumonia every minute. About 60% of pneumonia cases in the developing world are caused by bacteria and can be treated with antibiotics, whereas most cases of pneumonia in developed countries are viral.

A new study which shows that treating children with severe pneumonia at home is just as effective as treating them in hospitals could significantly change the way the illness is managed in developing countries, saving a significant number of lives every year and taking pressure off health systems.

Researchers from Boston University School of Public Health, supported by the World Health Organization (WHO) and U.S. Agency for International Development (USAID) conducted a study in Pakistan involving 2037 children with severe pneumonia who were randomly assigned to get either injectable antibiotics in a hospital or antibiotic pills at home. The trial was the first to compare the outcomes of hospital treatment of severe pneumonia with home-based treatment, and the results demonstrated the safety and efficacy of treating it with oral antibiotics outside of a hospital setting.

In the study, there were 87 (8.6%) treatment failures in the hospitalized group, and 77 (7.5%) in the group treated at home. Of the five children (0.2%) who died during the study, four were in the hospitalized group and one was at home.

This study confirmed the findings of three other trials at sites in Africa, Asia, Europe and Latin America, which showed that oral antibiotics were just as effective as injectable antibiotics in treating hospitalized children with severe pneumonia.

"The potential impact of these results is enormous," said the article's co-author Dr Shamim Qazi, Medical Officer with the WHO's Department of Child and Adolescent Health and Development. "Effective management of pneumonia is critical to improving child survival. Being able to treat children with severe pneumonia safely and effectively in their own homes would be of huge benefit to both families and health systems, by reducing the need for admission to hospital".

Similar research studies, if implemented into programs around the globe, is expected to increase access to critical care in disadvantaged communities and could support the potential to diagnose and treat severe pneumonia by community health workers.

The current guidelines advise health workers to provide oral antibiotics for cases of non-severe pneumonia and to refer severe and very severe cases to hospitals for treatment with antibiotics by injection. However, many children with severe pneumonia who are currently referred for admission to a hospital either die before they reach there or are so sick by the time they arrive that nothing more can be done to save them.

A small number of cases of very severe pneumonia (around 2-3% of all pneumonia cases) will still require treatment with injectable antibiotics in a hospital.

Families in the poorest countries, where the

majority of children are affected by pneumonia, may not have easy access to hospitals. In-patient treatment may not be an option for parents who cannot leave their homes to accompany the sick child. In addition, children with severe pneumonia are vulnerable to infections as a result of weak immunity and could be at increased risk in crowded hospital wards. A community-based approach would bring treatment to people's homes, so that children with pneumonia can be identified and begin treatment before the onset of life-threatening complications.

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