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From the Editor

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This is the last issue this year of the journal. The issue has papers from various countries in the region dealing with various topics. In addition with this issue we are Introducing the Middle East Primary Care Quality Improvement program (MEQUIP). See www.mejfm/MEQUIP/index.htm

A paper from Yemen attempt to describe epidemiological and clinical features of cutaneous leishmana cases. It was a retrospective descriptive records review of all patients with cutaneous leishmaniasis diagnosed at the Seiyun general hospital from January to December 2013.

A total of 122 patients were diagnosed with cutaneous leishmaniasis. The age of patients ranged between 1 to 62 years and the mean age is 26.5 ± 18.1 years. Most of the patients 56(45.9%) were of age group less than 20 years. The most common type of lesions were nodulo-ulcerated 52(42.7%) followed by nodular 45(36.9%). The distribution of sex, in which males and females of age group less than 20 years, were predominant 38 (31.1%) and 18 (14.8%) respectively. The authors concluded that that Wadi Hadramout is an endemic region of leishmaniasis and our findings will be of great interest to the public health authorities in Hadramout.

A paper from Turkey investigated the possibility that t Digital clubbing may be a pioneer sign of cirrhosis in sickle cell patients. All patients with SCDs were taken into the study. The study included 397 patients (193 females and 204 males). There were 36 patients (9.0%) with digital clubbing. The male ratio was significantly higher in the digital clubbing group (66.6% versus 49.8%, $p<0.05$). The author concluded that SCDs are chronic catastrophic processes on endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Digital clubbing may show an advanced disease and be a pioneer sign of cirrhosis in such patients.

A paper from Iraq was designed to compare the effectiveness of different angiotensin inhibitors; direct rennin inhibitor (Aliskiren), angiotensin-converting enzyme inhibitors (Ramipril) and angiotensin II receptor blocker (Irbesartan) in prevention and treatment of nephropathy in a group of rat diabetic nephropathy in rats. Diabetic nephropathic rats showed a significant increase in blood glucose level, blood pressure, heart rate, serum urea, serum creatinine, in addition to deteriorating renal functions including (urine flow, glomerular filtration rate, Na+ and K+ excretion rate, albumin and creatinine in the urine). The administration of (Ramipril, Irbesartan, and Aliskiren) caused a significant reduction in blood pressure, blood glucose, serum urea, Na+ and K+ excretion rate, with a significant improvement in urine flow and glomerular filtration rate. All three drugs induced a significant elevation in serum K+ concentration. The authors concluded that administration of different angiotensin inhibitors (ramipril, irbesartan, & aliskiren) could slow the progression of nephropathy in alloxan induced diabetic rats. Both ramipril and irbesartan have the same renoprotective effects for most parameters.

A review paper form Lebanon looked at obesity Management in Primary Health Care. The author stressed that Obesity is a key public health problem across the world. Easy solutions are unlikely, given the complex interaction between the abundant availability of energy dense food, the ever decreasing demand for energy expenditure in the modern world. This review paper address the issues of overweight and obesity in primary health care.

Renoprotective evaluations of different angiotensin inhibitors on Diabetic Nephropathy in Rats

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ABSTRACT

Background: **This study was designed to compare the effectiveness of different angiotensin inhibitors; direct renin inhibitor (Aliskiren), angiotensin-converting enzyme inhibitors (Ramipril) and angiotensin II receptor blocker (Irbesartan) in prevention and treatment of nephropathy in a group of rat diabetic nephropathy in rats.**

Methods: **Thirty rats were divided into two groups. The first group consisted of 6 rats which were considered as the normal control group. The second group included 24 induced diabetic rats. The diabetic model rats were subdivided into four subgroups of six rats each. The first subgroup served as a positive control. The second, third and fourth subgroup received Ramipril, Irbesartan and Aliskiren respectively.**

Results: **Diabetic nephropathic rats showed a significant increase in blood glucose level, blood pressure, heart rate, serum urea, serum creatinine, in addition to deteriorating renal functions including (urine flow, glomerular filtration rate, Na+ and K+ excretion rate, albumin and creatinine in the urine). The administration of (Ramipril, Irbesartan, and Aliskiren) caused a significant reduction in blood pressure, blood glucose, serum urea, Na+ and K+ excretion rate, with a significant improvement in urine flow and glomerular filtration rate. All three drugs induced a significant elevation in serum K+ concentration.**

Conclusion: **Administration of different angiotensin inhibitors (ramipril, irbesartan, & aliskiren) could slow the progression of nephropathy in alloxan induced diabetic rats. Both ramipril and irbesartan have the same renoprotective effects for most parameters.**

Key words: **Diabetic nephropathy, Aliskiren, Irbesartan, Ramipril**

Introduction

Diabetic nephropathy is a major microvascular complication of diabetes, representing the leading cause of end stage renal disease in the world. Diabetic nephropathy is characterized by a progressive increase in urinary albumin excretion (microalbuminuria) and a decline in glomerular filtration rate (GFR), which occurs in association with an increase in blood pressure, ultimately leading to end stage renal disease (1, 2).

Basic and clinical research supports the use of renin angiotensin aldosterone system (RAAS) inhibitors in diabetic nephropathy (3, 4, 5).

Several basic and clinical studies, mainly in diabetic patients, have provided evidence that some antihypertensive agents that inhibit the renin angiotensin aldosterone system (RAAS), like angiotensin II type 1 receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEI), are renoprotective (6, 7). The reno-protection provided by these drugs seems at least partly independent of BP lowering and related perhaps to the inhibition of the RAS (8, 9, 10).

Several mechanisms participate in the renal protection afforded by angiotensin inhibitors. ACEIs increase the permeability selectivity of the filtering membrane, thereby diminishing exposure of the mesangium to proteinaceous factors that may stimulate mesangial cell proliferation and matrix production, two processes that contribute to expansion of the mesangium in diabetic nephropathy. Since angiotensin II is a growth factor, reductions in the intrarenal levels of angiotensin II may further attenuate mesangial cell growth and matrix production (11, 12, 13).

Thus, there do not appear to be significant differences between ACEI and ARBs in type 2 diabetic patients with nephropathy based on a small number of comparison studies.

Other studies in hypertensive type 2 diabetics with early nephropathy comparing ACEIs and ARBs have also failed to show significant differences in the effects of these two drug classes on BP and urinary albumin excretion (14, 15). Only a few studies have addressed the question of whether ACE inhibitors are better than ARBs or vice versa.

This study is designed to compare the effectiveness of different angiotensin inhibitors, direct renin (DR) inhibitor (Aliskiren), ACEI (Ramipril) ARBs (Irbesartan) in prevention and treatment of nephropathy in rat induced diabetes.

Materials and Methods

Animals

Healthy adult albino rats of both sexes were used in the present study. Their weight ranged from 250-300 grams. Rats were grouped and kept in separate animal cages at the animal house of the College of Medicine under prevailing atmospheric conditions (room temperature of about 25c).

The animals were maintained on a balanced diet (bread, barley, carrots, lettuce, milk) and fresh-water supply.

Induction of experimental diabetes

Diabetes was induced by a single intraperitoneal injection of 120mg/kg body weight of alloxan dissolved in distilled water immediately before injection 16. Alloxan treated animals were allowed to drink 5% of glucose overnight to prevent the potentially fatal hypoglycemia occurring as a result of massive insulin release following alloxan injection (17).

Rats showing blood glucose levels above 180 mg/dl were considered to be diabetic (18) and used for drug treatment.

Experimental design

Thirty rats were divided into five groups each consisting of 6 rats in order to study the effect of different angiotensin inhibitors (Ramipril, Irbesartan, Aliskiren) during the 21 days study period:

Group I: Normal control rats given D.W

Group II: Control diabetic rats given D.W

Group III: Diabetic rats given Ramipril 10mg/kg.

Group IV: Diabetic rats given Irbesartan 10mg/kg.

Group V: Diabetic rats given Aliskiren 10 mg/kg.

The solution of drugs was freshly prepared in normal saline before administration by an oral gavage every morning.

Collection of samples

1-Urine

After 3 days, and at the end of drug treatment, all of the animals were kept in metabolic cages. Animals were fasted but allowed free access to water. Urine sample were collected after 24 hours in urine collecting bottles from which the urine collected was tested for: Albumin, Creatinine, Na+ excretion rate and K+ excretion rate, glomerular filtration rate and others.

2-Blood

At the end of drug treatment, all of the animals were fasted overnight but allowed free access to water. The next morning, blood samples were taken by cardiac puncture into a plastic syringe under a combination of ketamine in a dose of 75 mg/kg with xylazine in a dose of 10 mg/kg. At 10th day and at the end of experiment (after 21 days), a 24 hours urine collection was carried out by using the metabolic cage. The urine was checked for the albumin and total protein by using Cybow diagnostic kits (DFI co. Ltd, Gimhae- City, Gyung- Nam, Korea).

Statistical Analysis

All data are expressed as the mean ± standard error means (M ± SEM). The results were evaluated by using the Statistical Package for the Social Sciences (SPSS Version 21) computer program and the differences in all parameters between diabetic and non-diabetic rats were analyzed by a

one-way analysis of variables (ANOVA). The comparison between groups was done using Duncan test. A change was considered statistically significant when P<0.05.

The experiments were carried out with the approval of the ethic committee of Hawler Medical University/college of Medicine.

Results

Effect of Ramipril, Irbesartan, and Aliskiren on the blood pressure and heart rate of diabetic rats.

In alloxan-induced diabetic rats, a significant high elevation in blood pressure was seen when compared to the normal control group, Table 1. The heart rate of diabetic rats was moderately higher than that of the normal control. A significant reduction in blood pressure was observed following oral 10 mg/kg administration of all the angiotensin inhibitors (Ramipril, Irbesartan, and Aliskiren) when compared to the diabetic group. Table (1).

Ramipril and aliskiren treated group had a significant reduction in their heart rate, while irbesartan caused non-significant changes when compared to the diabetic group.

Effect of angiotensin inhibitors on the renal function of diabetic rats

The urine flow of the diabetic rats was significantly higher than the normal control group. Aliskiren caused a significant reduction in the urine flow when compared to the diabetic rats, while ramipril, and irbesartan produced a non-significant reduction in the urine flow when compared with both groups. While the glomerular filtration rate (GFR) of diabetic rats was found to be significantly lower than normal rats. Angiotensin inhibitors (Ramipril, Irbesartan, & Aliskiren) induced a significant improvement in the GFR when compared to the diabetic group Table (2) - next page.

In alloxan-induced diabetic rats there was a marked elevation in albuminuria when compared to the control animals. Daily oral administration of angiotensin inhibitors for 21 days caused a significant reduction in albumin excreted through urine when compared to the diabetic group.

The effect of different angiotensin inhibitors on Na+ concentration in the urine, were non-significantly reduced in comparison to the diabetic animals, although the urinary Na+ concentration did not return to the normal value. Table (3). The Irbesartan treated rats did not show a significant improvement in Na+ excretion rate, while Ramipril and Aliskiren treated rats induced a significant reduction in Na+ excretion rate. As shown in Table (3) there was a significant reduction in Na+ serum concentration level of angiotensin inhibitors treated rats when compared to the diabetic rats. In comparison to the diabetic rats, the percentage of Na+ reabsorption in the angiotensin inhibitors treatment groups were non-significantly reduced. Table (3) - next page.

Effect of angiotensin inhibitors on the renal excretion of K+ of the diabetic rats

Following the induction of diabetes by alloxan, there was a reduction in K+ urine concentration accompanied by an increase in the urinary potassium excretion rate. There was a significant elevation in K+ urine concentration in the groups which received different angiotensin inhibitors in comparison with diabetic group.

The angiotensin inhibitor treated rats showed a significant decrease in the K+ excretion rate in comparison to the diabetic rats, albeit not reaching the normal range. The serum concentration of K+ was increased significantly in diabetic and treated rats with angiotensin inhibitors when compared to the control group. Table (4) - page 7.

Table 1: The effects of 10 mg/kg of angiotensin inhibitors on the blood pressure & heart rate of the diabetic rats

Parameters	Control (n=6)	Diabetes (n=6)	Ramipril (n=6)	Irbesartan (n=6)	Aliskiren (n=6)
Blood pressure (mm.Hg)	102.1 ± 5.48 a	135.76 ± 6.43 b	106.56 ± 3.44 a	106.2 ± 3.88 a	112.34 ±3.004 a
Heart rate (Beats/min)	297.33 ± 4.73 a	352.11 ±10.97 b	312.2 ± 16.4 a	323.4 ± 13.16 ab	310.8 ± 12.7 a

* Similar letters indicate no significant differences.

* Different letters indicate significant differences at P < 0.05.

Table 2: The effects of 10 mg/kg of angiotensin inhibitors on the urine flow, GFR, and albuminuria of the diabetic rats

Parameters	Control (n=6)	Diabetes (n=6)	Ramipril (n=6)	Irbesartan (n=6)	Aliskiren (n=6)
Urine flow (ml/min/kg)	0.014 ±0.00216 a	0.034 ± 0.0054 b	0.023 ± 0.006 ab	0.022 ± 0.0033 ab	0.018 ± 0.0038 a
GFR (ml/min/kg)	0.065 ± 0.0123 a	0.025 ± 0.0065 b	0.037 ±0.0089 a	0.038 ±0.0085 a	0.033 ± 0.0047 a
Albumin in urine (mg/dl)	110 ± 40.49 a	500 ± 91.24 b	153.3 ± 14.75 a	155 ± 47.17 a	166.66 ± 42.6 a

* Similar letters indicate no significant differences.

* Different letters indicate significant differences at $P < 0.05$.

Table 3: Effects of angiotensin inhibitors on the renal excretion of Na+ of the diabetic rats

Parameters	Control (n=6)	Diabetes (n=6)	Ramipril (n=6)	Irbesartan (n=6)	Aliskiren (n=6)
Na+ in urine (mEq/dl)	82.3 ± 7.5 a	165 ± 8.96 b	134.166 ±23.88 b	131.66 ±18.28 b	124.5 ± 16.7 b
Na^+ excretion rate (mEq/min/kg)	2.14 ± 0.528 a	5.077 ± 0.78 b	2.367 ± 0.23 a	3.88 ± 0.67 b	2.15 ± 0.33 a
S. Na^+ Concentration (mEq/L)	138.16 ± 18.9 a	215.16 ± 32.65 b	149.5 ± 21.2 a	153.7 ±33.3 a	146.8 ± 17.73 a
% Na^+ reabsorption of filtered load	70.88 ± 4.85 a	95.67 ± 14.57 b	79.55 ± 5.3 ab	83.77 ± 4.71 ab	84.8 ± 4.18 ab

* Similar letters indicate no significant differences.

* Different letters indicate significant differences at $P < 0.05$.

Table 4: Effects of different angiotensin inhibitors on the renal excretion of K+ of the diabetic rats

Parameters	Control (n=6)	Diabetes (n=6)	Ramipril (n=6)	Irbesartan (n=6)	Aliskiren (n=6)
K^+ in urine (mEq/dl)	87.5 ± 15.47 a	66.5 ± 3.6 b	78.3 ±10.14 a	81.46 ± 9.54 a	83.66 ± 8.79 a
K^+ excretion rate (mEq/ min/kg)	1.194 ± 0.23 a	2.53 ± 0.41 b	1.31 ± 0.24 a	1.225 ± 0.3 a	1.35 ± 0.29 a
S. K^+ conc. (mEq/L)	4.16 ± 0.24 a	4.8 ± 0.61 b	5.7 ± 0.33 b	5.9 ± 0.35 b	5.15 ± 0.42 b

* Similar letters indicate no significant differences.

* Different letters indicate significant differences at $P < 0.05$.

Table 5: Effect of angiotensin inhibitors on the biochemical parameters of the diabetic rats

Parameters	Control n=6	Diabetes n=6	Ramipril n=6	Irbesartan n=6	Aliskiren n=6
Blood glucose (mg/dl)	106.2 ±10.99 a	237.2 ±34.63 b	130.16 ±6.37 a	126.43 ±5.23 a	114 ± 7.98 a
S.Urea (mg/dl)	30.42 ± 3.55 a	44.19 ± 2.21 b	35.2 ± 2.36 a	33 ± 3.38 a	35.7 ±1.74 a
S.Creatinine (mg/dl)	0.76 ± 0.044 a	1.296 ± 0.17 b	1.12 ± 0.04 b	1.14 ± 0.044 b	1.13 ±0.044 b

* Different letters indicate significant differences at $P < 0.05$

Effect of angiotensin inhibitors on the biochemical parameters (blood glucose, serum urea, & serum creatinine) of the diabetic rats

Following the treatment of diabetic animals with angiotensin inhibitors Ramipril, Irbesartan, and Aliskiren at a dose of 10 mg/kg for 21 days, a significant reduction in the blood glucose and serum urea were noticed when compared to the diabetic group. The ramipril, irbesartan, and aliskiren did not significantly change the serum creatinine in comparison to the diabetic rats. Table (5).

Discussion

Several randomized trials have shown that improved glycemic control in both type 1 and 2 diabetic patients decreases the risk of diabetic nephropathy and other complications. Although significant improvement in the treatment of diabetic nephropathy has occurred over the past 25 years, as a result, pharmacological inhibition of the RAS has been proposed as a key strategy in reducing kidney damage beyond the predicted effects as a result of blood pressure reduction. (19, 20, 21).

In diabetic rats, a definite and elevated blood pressure was seen when compared to the normal control group, while the heart rate of diabetic rats was moderately higher than that of the normal group. The result obtained from experiments on rats through detecting the effect of (Ramipril, Irbesartan, and Aliskiren) on blood pressure and heart rate, showed that there was a statistically significant decrease in blood pressure with a non-significant decrease in heart rate. Ramipril and irbesartan were better than aliskiren in decreasing Blood pressure. The hypotensive effect of different angiotensin inhibitors may be explained by the vasodilating effects of ACEI on the glomerular efferent arterioles, where it prevents the Ang-II formation (22). Inhibition of angiotensin lowers systemic vascular resistance and blood pressure; this is not surprising when the renal vessels are exceptionally sensitive to the vasoconstrictor actions of angiotensin II (23). Angiotensin inhibitor increases renal blood flow without increasing GFR; thus reducing the filtration fraction. Both the afferent and efferent arterioles are dilated as well

as causing systemic arteriolar dilatation. ACEI increases the compliance of large arteries, which contributes to systolic pressure reduction (24).

The urine flow of the diabetic rats was significantly higher than the normal control group, while the glomerular filtration rate (GFR) of diabetic rats was found to be significantly lower than in the normal rats. In the present study, the result obtained from the experiment on rats for detecting the effect of different angiotensin inhibitors (Ramipril, Irbesartan, and Aliskiren) on urine flow and glomerular filtration rate, showed a significant improvement in the urine flow and GFR. Both ramipril and irbesartan had a superior renoprotective effect than that of aliskiren. The renal protection effect of different angiotensin inhibitors may be explained by ACEI probably attenuating the progression of renal insufficiency in patients with a variety of nondiabetic nephropathies, and may arrest the decline in GFR even in patients with severe renal disease (25, 26, 27). Normally, GFR is slightly reduced by angiotensin II; however, during renal artery hypotension, the effects of angiotensin II on the efferent arteriole predominate, leading to increased renal blood flow, hence increasing GFR. Therefore, blockade of the renin-angiotensin system may cause acute renal failure in patients with bilateral renal artery stenosis and in patients with unilateral stenosis who have only a single kidney (7). Angiotensin II variably influences GFR via several mechanisms such as constricting the afferent arterioles, which reduces intra-glomerular pressure and GFR, or by contracting the mesangial cells, which decreases the capillary surface area within the available glomerulus which subsequently leads to decrease GFR, and it could be due to constricting effect on the efferent arterioles, which increases intra-glomerular pressure which increases GFR (28, 29).

The result of this experiment is in agreement with a study by Weidmann et al (1995) who concluded that GFR is better preserved in ACEI treated groups (30). Furthermore, Lebovitz et al (1996) (31) declared that enalapril prevented falling in GFR in hypertensive patients. However, the result of the present study does not agree with Kasiske et al (1993) who found that ACEI is more superior to B blockers in decreasing GFR among diabetic patients (32). Parving and Rossing (1994)) concluded that lisinopril has no significant effects in decreasing GFR in diabetic nephropathic patients 33 . Moreover, Barnett et al (2005) showed that the rate of GFR decrease was equivalent in both enalapril and telmisartan treated patients (34).

In the present study a marked elevation in albuminuria was seen in diabetic rats. Increased glomerular pressure associated with diabetes can be enhanced by aII-mediated constriction of the glomerular arterioles, causing further elevation in microcirculatory pressure within the glomerulus, and leading to excretion of albumin, and thus to the development of microalbuminuria and proteinuria (35). While after the oral administration of (ramipril, irbesartan and aliskiren) a significant reduction in urinary albumin was noticed. In addition, both ramipril and irbesartan better reduced the albumin in the urine. This result is in agreement with studies conducted by Chan et al (2000), and Jerums et al (2001) who reported that treatment with ACEI & aliskiren decrease albumin excretion rate (36, 37).

Studies in streptozotocin diabetic rats have demonstrated that both AIIB and ACEi blocked the development of hypertension and significantly decreased albuminuria 38. Whereas in the DETAIL (Diabetic exposed to telmisartam and enalapril) study there were no significant differences in albumin excretion rate in both enalapril and telmisartan treated patients (34).

Several mechanisms have been suggested for antiproteinuric effects of RAS inhibition. First, it may be related to a reduction in intraglomerular blood pressure independently of systemic blood pressure by vasodilatation preferentially of the postglomerular arterioles (39). Second, RAS inhibition may improve the charge and size selectivity of the glomerular membrane (40), which may be related, in part, to reduced loss of glomerular nephrin, which has been suggested to play a central role in the function of the glomerular filtration barrier (41).

The administration of both ramipril and aliskiren induced a significant change in Na+ excretion rate, while irbesartan did not show any significant improvement in diabetic rats. On the other hand the effect of ramipril, irbesartan, and aliskiren on the Na+ concentration in the urine was non-significant.

There was a non - significant reduction in the level of serum Na+ concentration in all treated rats. The percentage of Na+ reabsorption in the angiotensin inhibitor treatment group was non - significantly reduced but still lower than the control group.

However, it has been suggested that angiotensin II can act presynaptically to potentiate the release of norepinephrine from sympathetic nerve terminals and thus enhancing the renin release from the renal tubule (42, 43). The rise in sodium level in diabetic rats could be related to the fact that angiotensin II stimulates the zona glomerulosa of the adrenal cortex to increase the synthesis and secretion of aldosterone which acts on the distal and collecting tubules to cause retention of Na+ and excretion of K+ and H+. The stimulant effect of angiotensin II on aldosterone synthesis and release is enhanced under conditions of hyponatremia or hyperkalemia and reduced when concentrations of Na+ and K+ in plasma are altered in the opposite directions (44). Very low concentrations of angiotensin II stimulate Na+/H+ exchange in the proximal tubule; an effect that increases Na+, Cl-, and angiotensin II may reduce Na+ excretion in part by diminishing medullary blood flow.

In the present study, the significant decrease in the K+ excretion rate accompanied by a non-significant rise in the serum K+ level were detected following administration of ramipril, irbesartan, and aliskiren. These effects could be explained by suppression of endogenous aldosterone and worsening kidney function (45). Despite some reduction in the concentration of aldosterone, significant K+ retention is rarely encountered in patients with normal renal function who have not been taking other drugs that cause K+ retention (46).

In this study, the level of blood glucose in diabetic rats was significantly increased when compared to the control group. This result in accordance with studies of Bilal et al (1998), Azuma

et al (2007) who suggested that elevated blood glucose levels in diabetes are caused by a defect in production and or secretion of the hormone insulin (47, 48). In this study the elevation of blood glucose level indicate that this effect is caused by the direct influence of alloxan on pancreatic beta cells.

Treatment with angiotensin inhibitors Ramipril, Irbesartan, and Aliskiren caused a significant reduction in the blood glucose level of diabetic rats. However, aliskiren was better in reducing blood glucose than the other two drugs.

In this study the hypoglycemic effect of angiotensin inhibitors may be due to increased rate of glucose uptake into the cell, and to improve glucose metabolism (49, 50). Clarification of the mechanism of this effect is in progress. In patients with essential hypertension, plasma insulin and blood glucose levels increase together, indicating reduced insulin sensitivity. Because of this, even without the onset of diabetes, a latent rise in blood glucose level may be seen. Angiotensin receptor blocker and ACEI can improve glucose metabolism via blocking the inhibitory effect of angiotensin II on insulin signal transmission (51, 52). On the other hand, the vasodilatory action of angiotensin inhibitor may increase the access of insulin and glucose to the skeletal muscle tissue, the main site of insulin-mediated removal of glucose 53. The result of hypoglycemic effects of ramipril, irbesartan, and aliskiren in the diabetic rats is in agreement with other studies done by Jacobsen et al (2003), Lau et al (2004), Dizaye and Rashid (2009) (54, 55, 56). Subsequent studies indicated that telmisartan also suppressed the new onset of diabetes (53).

In the present study ramiprl, irbesartan, and aliskiren did not significantly decrease serum creatinine, and this effect was compatible with the finding of Lewis et al (2001) who suggested that the level of serum creatinine was not significantly changed by irbesartan in nephropathic patients (21). Along the same lines, are the data from other studies which showed that serum creatinine levels did not significantly change in the ACEI group (57, 58). However, the result of this study was in disagreement with the study of Brenner et al (2001), who found that there was 25% reduction for doubling the serum creatinine level after using ACEi (20).

Conclusion

Administration of different angiotensin inhibitors (ramipril, irbesartan, and aliskiren) could slow the progression of nephropathy in alloxan induced diabetic rats. Both ramipril and irbesartan had the same renoprotective effects for most parameters.

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Digital clubbing may be a pioneer sign of cirrhosis in sickle cell patients

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ABSTRACT

Background: **Sickle cell diseases (SCDs) are chronic destructive processes on endothelium initiating at birth all over the body. We tried to understand whether or not there is a relationship between digital clubbing and severity of SCDs.**

Methods: **All patients with SCDs were taken into the study.**

Results: **The study included 397 patients (193 females and 204 males). There were 36 patients (9.0%) with digital clubbing. The male ratio was significantly higher in the digital clubbing group (66.6% versus 49.8%, p<0.05). The mean age was significantly higher in the digital clubbing group too (36.5 versus 29.0 years, p=0.000). Similarly, smoking was also higher in the digital clubbing group, significantly (30.5% versus 11.0%, p<0.001). Beside that, prevalence of cirrhosis (25.0% versus 1.6%, p<0.001), leg ulcers (33.3% versus 11.9%, p<0.001), pulmonary hypertension (27.7% versus 9.6%, p<0.001), chronic obstructive pulmonary disease (38.8% versus 12.1%, p<0.001), coronary heart disease (27.7% versus 12.1%, p<0.01), and stroke (27.7% versus 6.9%, p<0.001) were all higher in the digital clubbing group, significantly. Although the mean white blood cell counts of peripheric blood were similar in both groups, the mean hematocrit value and platelet count were lower in the digital clubbing group, probably due to the effects of cirrhosis, significantly (p= 0.001 and p= 0.012, respectively).**

Conclusion: **The SCDs are chronic catastrophic processes on endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Digital clubbing may show an advanced disease and be a pioneer sign of cirrhosis in such patients.**

Key words: **Sickle cell diseases, chronic endothelial damage, atherosclerosis, digital clubbing, cirrhosis**

Introduction

Chronic endothelial damage induced atherosclerosis may be the major cause of aging by causing disseminated tissue ischemia all over the body. For example, cardiac cirrhosis develops due to the prolonged hepatic hypoxia in patients with pulmonary and/or cardiac diseases. Probably whole afferent vasculature including capillaries are involved in atherosclerosis. Some of the currently known accelerator factors of the inflammatory process are physical inactivity, overweight, and smoking for the development of irreversible end points including obesity, hypertension (HT), diabetes mellitus (DM), peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), coronary heart disease (CHD), cirrhosis, mesenteric ischemia, osteoporosis, and stroke, all of which terminate with early aging and death. They were extensively researched under the issue of metabolic syndrome in the literature (1,2). Similarly, sickle cell diseases (SCDs) are chronic catastrophic processes on endothelium particularly at the capillary level. Hemoglobin S (HbS) causes loss of elasticity and biconcave disc shaped structures of red blood cells (RBCs). Probably, loss of elasticity instead of shapes of RBCs is the major problem, since sickling is very rare in the peripheric blood samples of the SCDs patients with associated thalassemia minors, and human survival is not so affected in hereditary elliptocytosis or spherocytosis. Loss of elasticity is probably present in whole lifespan, but exaggerated with increased metabolic rate of the body. The hard cells induced lifelong endothelial inflammation, edema, remodeling, and fibrosis mainly at the capillary level and terminate with generalized tissue hypoxia all over the body (3,4). On the other hand, obvious vascular occlusions may not develop in greater vasculature due to the transport instead of distribution function of them. We tried to understand whether or not there is a relationship between digital clubbing and severity of SCDs in the present study.

Material and Methods

The study was performed in Medical Faculty of the Mustafa Kemal University between March 2007 and March 2015. All patients with the SCDs were studied. The SCDs are diagnosed with hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC) method. Medical histories including smoking habit, regular alcohol consumption, painful crises per year, surgical operations, priapism, leg ulcers, and stroke were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A check up procedure including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C and human immunodeficiency virus, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure the systolic blood pressure (BP) of pulmonary artery, an abdominal ultrasonography, a computed tomography of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed by means of MRI (5). Cases with acute painful crises or any other inflammatory event were treated at first, and then the laboratory tests and clinical measurements were performed on the silent phase. Stroke is diagnosed by the computed tomography of brain. Acute chest syndrome is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia in the patients (6). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention and discomfort, vomiting, obstipation, and lack of bowel movement. The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/forced vital capacity of less than 70% (7). Systolic BP of the pulmonary artery of 40 mmHg or higher during the silent period is accepted as pulmonary hypertension (8). CRD is diagnosed with a serum creatinine level of 1.3 mg/dL or higher in males and 1.2 mg/dL or higher in females during the silent period. Cirrhosis is diagnosed with liver function tests, ultrasonographic findings, and histologic procedure in case of indication. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is greater than 1.0 and with the presence of Schamroth's sign (9,10). Associated thalassemia minors are detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC method. Stress electrocardiography is just performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken just for the stress electrocardiography positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Ileus is diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity of the abdomen. Eventually, cases with digital clubbing and without were collected into the two groups, and they were compared in between. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 397 patients with the SCDs (193 females and 204 males). There were 36 patients (9.0%) with digital clubbing. Mean age of patients was significantly higher in the digital clubbing group (36.5 versus 29.0 years, p=0.000). The male ratio was significantly higher in the clubbing group, too (66.6% versus 49.8%, p<0.05). Parallel to the male ratio, smoking was also higher in the digital clubbing group, significantly (30.5% versus 11.0%, p<0.001). Prevalences of associated thalassemia minors were similar in both groups (58.3% versus 66.2% in the clubbing group and other, respectively, p>0.05) (Table 1). On the other hand, prevalence of cirrhosis (25.0% versus 1.6%, p<0.001), leg ulcers (33.3% versus 11.9%, p<0.001), pulmonary hypertension (27.7% versus 9.6%, p<0.001), COPD (38.8% versus 12.1%, p<0.001), CHD (27.7% versus 12.1%, p<0.01), and stroke (27.7% versus 6.9%, p<0.001) were all higher in the digital clubbing group, significantly (Table 2). Although the mean white blood cell (WBC) counts of the peripheric blood were similar in both groups (p<0.05), the mean hematocrit (Hct) value and platelet (PLT) count of peripheric blood were lower in the digital clubbing group, probably due to the effects of cirrhosis, significantly (p= 0.001 and p= 0.012, respectively) (Table 3). There were 55 cases with leg ulcers, and 41 of them were male, so leg ulcers were much more common in males (20.0% in males versus 7.2% in females, p<0.001). Additionally,

Table 1: Characteristic features of the study cases

Variables	Cases with digital clubbing	*p*-value	Cases without digital clubbing
Prevalence	9.0% (36)		90.9% (361)
Male ratio	***66.6% (24)***	***<0.05***	***49.8% (180)***
Mean age (year)	***36.5 ± 10.9 (16-56)***	***0.000***	***29.0 ± 9.7 (5-59)***
Thalassemia minors	58.3% (21)	Ns*	66.2% (239)
Smoking	***30.5% (11)***	***<0.001***	***11.0% (40)***

*Nonsignificant (p>0.05)

Table 2: Associated pathologies of the study cases

Variables	Cases with digital clubbing	*p*-value	Cases without digital clubbing
Painful crises per year	5.0 ± 9.1 (0-36)	Ns*	5.2 ± 8.1 (0-52)
Tonsilectomy	2.7% (1)	Ns	8.0% (29)
Priapism	2.7% (1)	Ns	2.7% (10)
Ileus	8.3% (3)	Ns	3.3% (12)
Cirrhosis	***25.0% (9)***	***<0.001***	***1.6% (6)***
Leg ulcers	***33.3% (12)***	***<0.001***	***11.9% (43)***
Pulmonary hypertension	***27.7% (10)***	***<0.001***	***9.6% (35)***
COPD†	***38.8% (14)***	***<0.001***	***12.1% (44)***
CHD‡	***27.7% (10)***	***<0.01***	***12.1% (44)***
CRD§	11.1% (4)	Ns	7.2% (26)
Rheumatic heart disease	5.5% (2)	Ns	6.0% (22)
Avascular necrosis of bones	13.8% (5)	Ns	22.9% (83)
ACS¶	8.3% (3)	Ns	3.3% (12)
Stroke	***27.7% (10)***	***<0.001***	***6.9% (25)***
Mortality	8.3% (3)	Ns	6.0% (22)

*Nonsignificant (p>0.05) †Chronic obstructive pulmonary disease ‡Coronary heart disease §Chronic renal disease Acute chest syndrome

Table 3: Peripheric blood values of the study cases

Variables	Cases with digital clubbing	*p*-value	Cases without digital clubbing
Mean WBC* counts (/µL)	15.329 ± 4.801 (7.000-26.600)	Ns†	15.114 ± 6.756 (1.580-48.500)
Mean Hct‡ values (%)	*21.0 ± 4.3 (12-32)*	*0.001*	*23.9 ± 5.1 (8-42)*
Mean PLT§ counts (/µL)	*378.916 ± 184.460 (114.000-1.142.000)*	*0.012*	*461.116 ± 231.611 (48.800-1.827.000)*

*White blood cell †Nonsignificant (p>0.05) ‡Hematocrit §Platelet

there were five patients with regular alcohol consumption who are not cirrhotic at the moment. Although antiHCV was positive in eight of the cirrhotics, HCV RNA was detected as positive just in two, by polymerase chain reaction method.

Discussion

Chronic endothelial damage induced atherosclerosis may be the most common type of vasculitis, and the leading cause of morbidity and mortality in the elderly. Probably whole afferent vasculature including capillaries are involved in the body. Much higher BP of the afferent vasculature may be the major underlying cause, and efferent vessels are probably protected due to the much lower BP in them. Secondary to the prolonged endothelial damage and fibrosis, vascular walls become thickened; their lumens are narrowed, and they lose their elastic nature that can reduce the blood flow and increase BP further. Although early withdrawal of the causative factors including physical inactivity, excess weight, and smoking may prevent terminal consequences, after development of cirrhosis, COPD, CRD, CHD, PAD, or stroke, the endothelial changes may not be reversed completely due to the fibrotic nature of them (11).

SCDs are life-threatening genetic disorders affecting nearly 100,000 individuals in the United States (12). As a difference from other causes of atherosclerosis, the SCDs probably keep vascular endothelium particularly at the capillary level (13), since the capillary system is the main distributor of the hard RBCs to tissues. The hard cells induced chronic endothelial damage, inflammation, edema, and fibrosis build up an advanced atherosclerosis in much younger ages of the patients. In other words, SCDs are mainly chronic inflammatory disorders, and probably the major problem is endothelial damage, inflammation, edema, and fibrosis induced occlusions in the vascular walls rather than the lumens all over the body. As a result, the lifespans of patients with the SCDs were 48 years in females and 42 years in males in the literature (14), whereas they were 33.0 and 30.0 years in the present study, respectively. The great differences may be secondary to delayed initiation of hydroxyurea therapy and inadequate RBC transfusions in emergencies in our country. On the other hand, longer lifespan of females with the SCDs (14) and longer overall survival of females in the world (15) cannot be explained by the atherosclerotic effects of smoking alone, instead it may be explained by more physical power requiring role of male sex in life (16), since the physical power induced increased metabolic rate may terminate with an exaggerated sickling and atherosclerosis in body.

Digital changes may help to identify some systemic disorders in the body. For example, digital clubbing is a deformity of the finger and fingernails that has been known for centuries. It is characterized by loss of normal <165° angle between the nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (17). Schamroth's window test is a well-known test for the diagnosis of clubbing (10). The exact frequency of digital clubbing in the population is unknown, and some authors found clubbing in 0.9% of all patients admitted to the department of internal medicine (9), whereas the prevalence was 4.2% in both sexes in one of our studies (11). On the other hand, the exact underlying etiology of digital clubbing is unknown, but there are numerous theories about the issue, and chronic tissue hypoxia, vasodilation, secretion of growth factors, and some other mechanisms have been proposed (18-21). Moreover, the significance of diagnosing digital clubbing is not well established. For example, only 40% of digital clubbing cases turned out to have significant underlying diseases, while 60% had no medical problem on further investigations and remained well over the subsequent years (9). But digital clubbing is frequently associated with pulmonary, cardiac, and hepatic disorders that are featuring with chronic tissue hypoxia (9,11), since lungs, heart, and liver are closely related organs that affect their function in a short period of time. Similarly, hematologic disorders that are featuring with chronic tissue hypoxia may also terminate with digital clubbing. According to our observations, digital clubbing is probably an indicator of disseminated atherosclerosis particularly at the capillary level in the SCDs. For example, we observed clubbing in 9.0% of patients with the SCDs in the present study, and cirrhosis (25.0% versus 1.6%, p<0.001), leg ulcers (33.3% versus 11.9%, p<0.001), pulmonary hypertension (27.7% versus 9.6%, p<0.001), COPD (38.8% versus 12.1%, p<0.001), CHD (27.7% versus 12.1%, p<0.01), and stroke (27.7% versus 6.9%, p<0.001) like atherosclerotic end points were significantly higher among them. Similar to other studies, there was a male predominance in the clubbing group (66.6% versus 49.8%, p<0.05) that may also indicate role of smoking on clubbing (9,11).

Smoking may have a major role in systemic atherosclerotic processes such as COPD, digital clubbing, cirrhosis, CRD, PAD, CHD, stroke, and cancers (11,22). Its atherosclerotic effects are

the most obvious in Buerger's disease and COPD. Buerger's disease is an inflammatory process terminating with obliterative changes in small and medium-sized vessels and capillaries, and it has never been reported without smoking. COPD may also be a capillary endothelial inflammation terminating with disseminated pulmonary destruction, and it may be accepted as a localized Buerger's disease of the lungs. Although it has strong atherosclerotic effects, smoking in human beings and nicotine administration in animals may be associated with weight loss (23). There may be an increased energy expenditure during smoking (24), and nicotine may decrease caloric intake in a dose-related manner after cessation of smoking (25). Nicotine may lengthen intermeal time, and decrease amount of meal eaten in animals (26). Body weight seems to be the highest in former, lowest in current, and medium in never smokers (27). Since smoking may also show the weakness of volition to control eating, prevalences of HT, DM, and smoking were the highest in the highest triglyceride having group as a significant parameter of metabolic syndrome (28). Additionally, although CHD were detected with similar prevalences in both sexes (22), smoking and COPD were higher in males against the higher prevalences of body mass index and its consequences including dyslipidemia, HT, and DM in females.

Probably cirrhosis is also a systemic atherosclerotic process prominently affecting the hepatic vasculature, and aging, excess weight, smoking, alcohol consumption, infections, and other local or systemic inflammatory processes may be the major causes (29). The inflammatory process is enhanced with the release of various chemicals by lymphocytes to repair the damaged endothelium of hepatic vasculature (30), and the chronic inflammatory process terminates with an advanced atherosclerosis and tissue hypoxia in liver. Although cirrhosis is mainly thought to be an accelerated atherosclerotic process of the hepatic vasculature, there are close relationships between cirrhosis and digital clubbing, CHD, COPD, PAD, CRD, and stroke like other atherosclerotic end points (31). For example, most of the mortality cases in cirrhosis may actually be caused by cardiovascular diseases, and CHD may be the most common among them (32). Similarly, 25.0% of the digital clubbing cases were already cirrhotic, and the ratio was only 1.6% among the SCDs cases without clubbing in the present study ($p<0.001$). So beside the digital clubbing, CHD, COPD, leg ulcers, pulmonary hypertension, and stroke, cirrhosis may also be found among the terminal atherosclerotic end points of the SCDs (11,33).

Leg ulcers are seen in 10 to 20% of patients with the SCDs (34), and the ratio was 13.8% in the present study. The incidence increases with age and they are rare under the age of 10 years (34). Leg ulcers are also more common in males and sickle cell anemia (HbSS) cases (34). Similarly, there were 55 cases with leg ulcers, and 41 of them were male (20.0% in males versus 7.2% in females, $p<0.001$) in the present study. Additionally, mean ages of the patients with leg ulcers were significantly higher than the others (34.6 versus 28.7 years, $p<0.000$). They have an intractable nature, and around 97% of healed ulcers return in less than one year (35). The ulcers occur in distal areas with less collateral blood flow in the body (35). Chronic endothelial damage at the microcirculation due to the hard RBCs may be the major cause in the SCDs (34). Prolonged exposure to the causative factors due to the blood pooling in the lower extremities by the effect of gravity may also explain the leg but not arm ulcers in the SCDs. Probably the same mechanism is also true for diabetic ulcers, Buerger's disease, digital clubbing, varicose veins, and onychomycosis. Smoking may also have some additional roles for the ulcers (36), since both of them are much more common in males (34), and atherosclerotic effects of smoking are well-known (22). Venous insufficiency may also accelerate the process by causing pooling of causative hard RBCs in the legs. According to our eight-year experiences, prolonged resolution of ulcers with hydroxyurea therapy may also suggest that leg ulcers may actually be secondary to the increased WBC and PLT counts induced disseminated endothelial edema particularly at the capillary level.

Stroke is also a common complication of the SCDs (37), and thromboembolism in the background of accelerated atherosclerosis is the most common cause of it. Similar to the leg ulcers, stroke is higher in HbSS cases (38). Additionally, a higher WBC count is associated with a higher incidence of stroke (39). Sickling induced endothelial injury, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic endothelial inflammation, edema, remodeling, and fibrosis (40). Stroke in the SCDs may not have a macrovascular origin, instead disseminated endothelial edema may be much more important in the brain. Infections and other inflammatory processes may precipitate stroke, since increased metabolic rate may accelerate sickling and endothelial edema. Similar to the leg ulcers, a significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of strokes is secondary to the increased WBC and PLT counts' induced disseminated endothelial edema in the SCDs (13,41).

As a conclusion, SCDs are chronic catastrophic processes on endothelium particularly at the capillary level, and terminate with accelerated atherosclerosis induced end-organ failures in early years of life. Digital clubbing may show an advanced disease and be a pioneer sign of cirrhosis in such patients.

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Cutaneous Leishmania in Wadi Hadramout, Yemen

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ABSTRACT

Background: Cutaneous leishmaniasis is widespread in Yemen, but its extent has not been documented fully.

Objectives: The objective was to describe epidemiological and clinical features of cutaneous leishmana cases.

Methods: It was a retrospective descriptive records review of all patients with cutaneous leishmaniasis diagnosed at the Seiyun general hospital from January to December 2013.

Results: A total of 122 patients were diagnosed with cutaneous leishmaniasis. They were 73 (59.8%) males and 49 (40.2%) females with the ratio male to female 1.5:1.

The age of patients ranged between 1 to 62 years and the mean age is 26.5 ± 18.1 years.

Most of the patients 56(45.9%) were of age group less than 20 years.

The most common type of lesions were nodulo-ulcerated 52(42.7%) followed by nodular 45(36.9%).

The distribution of sex, in which males and females of age group less than 20 years, were predominant 38 (31.1%) and 18 (14.8%) respectively.

The rest of the patients, males and females, were convergent ($p > 0.05$).

The majority of lesions' site were lower limb 63 (51.6%) and the single lesions were predominant 76 (62.3%) also, the most lesion sizes were 0.5 cm 67 (54.9%) and 1 cm 50 (41%). Skin smears were positive in 102 (83.6%), negative in 9 (7.4%) and not done in 11 (9.0%) patients.

Conclusion: We concluded that Wadi Hadramout is an endemic region of leishmaniasis and our findings will be of great interest to the public health authorities in Hadramout.

Key words: Cutaneous Leishmania, Wadi Hadramout, Yemen

Introduction

Leishmaniasis is a parasitic disease caused by more than 20 species of protozoa of the genus Leishmania. It is transmitted by the bite of female sandflies of the genera Phlebotomus (Old World) and Lutzomyia (New World).

Pets and wild animals are the usual reservoir and source of the infection (zoonotic transmission), although the disease can also spread from human to human (anthroponotic transmission). The disease is endemic in more than 80 countries in Latin America, Asia, Africa, and Southern Europe (1). Other published literatures reported that Leishmaniasis is endemic in 88 countries with incidence rate of 1.5-2 million; the most common form of leishmaniasis is cutaneous leishmaniasis (CL) with 1.5 million new cases per year (2,3).

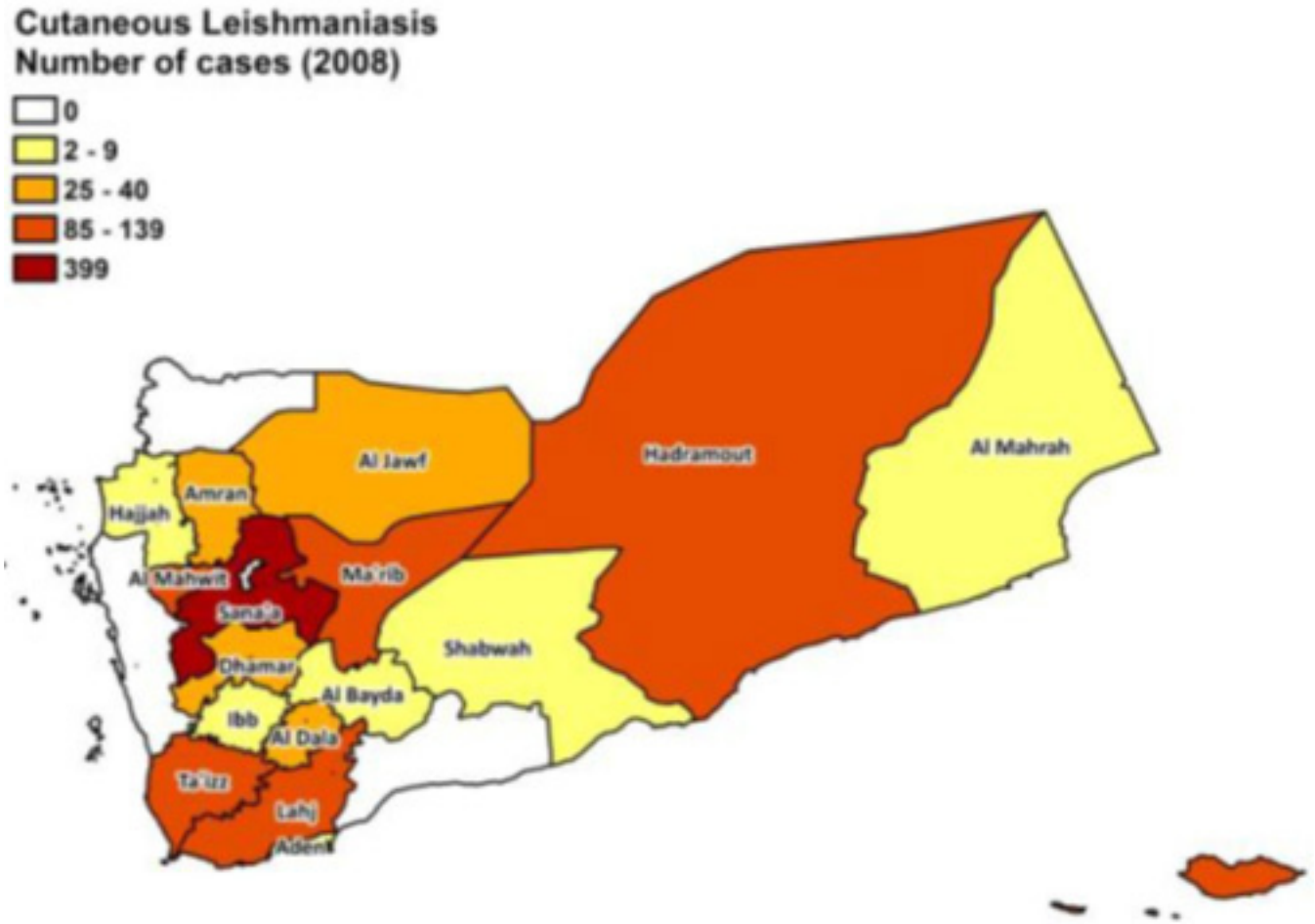
90% of cutaneous leishmaniasis are reported from Iran, Afghanistan, Algeria, Iraq, Saudi Arabia, and Syria in the Old World; and Bolivia, Brazil, Colombia, and Peru in the New World (4).

Yemen is a tropical country, poor, has lack of health care, and most of the population below the poverty line (5).

There are very few reports on leishmaniasis in Yemen in the international literature. Even though it is not well documented, the disease seems to be endemic in the country, and is primarily widespread in arid and semiarid areas. It is also endemic in the plateau and mountainous areas of Hadramout governorate (5).

Hadramout governorate lies in the eastern part of Yemen. The governorate comprises different topography distributed between coastal plains, mountains and hills of heights reaching 2000 m above sea level, large areas of Al-Ruba Al-khali desert, with many valleys; the largest Hadramout valley which is supplied by many branch valleys, is the longest valley and the most fertile in the Arab peninsula since it is 160km long and pours in Sihout on the Arab sea at Al-Mahra governorate. The climate in Hadramout is a hot tropical climate. Hadramout valley is considered one of the highest valleys in technology related to water courses drainage, as ducts water drainage are made within hours, which is not usual in many large valleys in Yemen where water courses continue running for a long time. Seiyun city located 322km from Mukalla, is the largest city in Hadramout valley and it is the administrative capital of the valley (6).

Figure 1: Cutaneous leishmaniasis



Objectives

To describe epidemiological and clinical features of cutaneous leishmania cases identified recently in Seiyun district, Hadramout, Yemen.

Materials and Methods

Study area:

The study was conducted in Seiyun general hospital which is the central hospital of Hadramout valley and located in Seiyun city, Hadramaut, Yemen.

The hospital is a tertiary health institution that renders medical care to its host community and environs.

It serves as a referral center for neighbouring areas which include cities of Hadramaut valley and the surrounding villages.

Study period

This study was performed during the period January to December 2013.

Study Design

A retrospective descriptive records review was conducted.

Study sample:

The study population consisted of all patients with cutaneous leishmaniasis diagnosed at the Seiyun general hospital from January 2013 to December 2013.

The diagnoses were made by consultant dermatologist, after reviewing the history, physical signs, clinical pictures and clinical investigations of the patients.

Permission was sought and obtained in writing from the director of the hospital and the head of the medical records department of the hospital to collect data from patient's case notes at the medical records center.

Data collection procedure:

Checklist was prepared for collection of data from patient record.

Data variables:

Data that were collected included the sex, age, type of lesion, site of lesion, number of lesions, size, result of skin smear and histopathology in few cases (when needed).

Data Analysis and Presentation:

The data was analyzed and tabulated through descriptive statistics using Microsoft Excel spreadsheet and SPSS version 17 statistical software.

Figure 2: The geographical location of Hadramout valley (Wadi Hadramout)

Source: http://www.istockphoto.com/photos/wadi-hadramout?sort=best&excludenudity=true&mediatype=photography&phrase=wadi%20hadramout

Results

In the study year 2013, a total of 122 patients were diagnosed with cutaneous leishmaniasis according to their medical records. They were 73 (59.8%) males and 49 (40.2%) females with the ratio male to female 1.5:1.

The age of patients ranged between 1 to 62 years. The mean age of the patients is 26.5 ± 18.1 years.

Most of the patients 56 (45.9%) were of age group less than 20 years followed by the age group 40 years and more 35 (28.7%).

The most common type of lesions were nodulo-ulcerated 52 (42.7%) followed by nodular 45 (36.9%), papulo-nodular 17 (13.8%), plaque 5 (4.1%) and ulcerated lesions 3 (2.5%) as shown in Table1 and Figures 3 to Figure 6.

Table 1: Variables of sex and Types of lesions (n = 122)

Variables	No	%
Sex:		
Males	73	59.8
Females	49	40.2
Age:		
< 20	56	45.9
20-39	31	25.4
≥ 40	35	28.7
Type of lesion:		
- Nodular ulceration	52	42.7
- nodular	45	36.9
- Papular nodular	17	13.8
- plaque	5	4.1
- Ulceration	3	2.5

Figure 3: Nodular-ulcerated lesion on nose

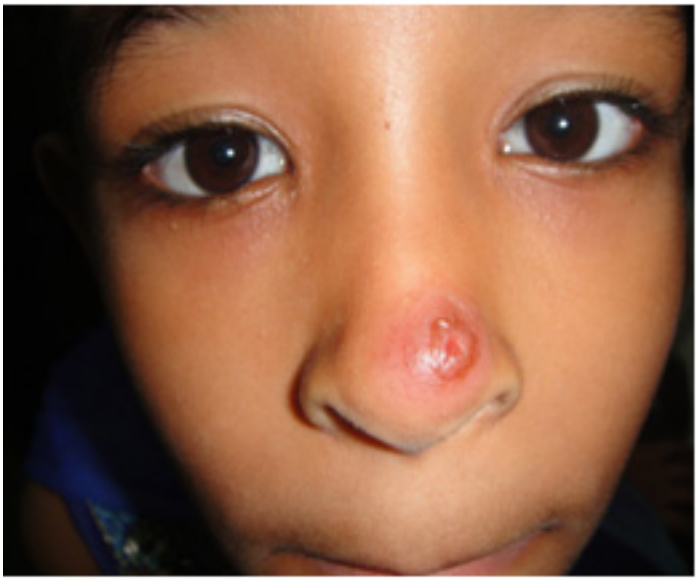


Figure 4: Nodular lesion on nose

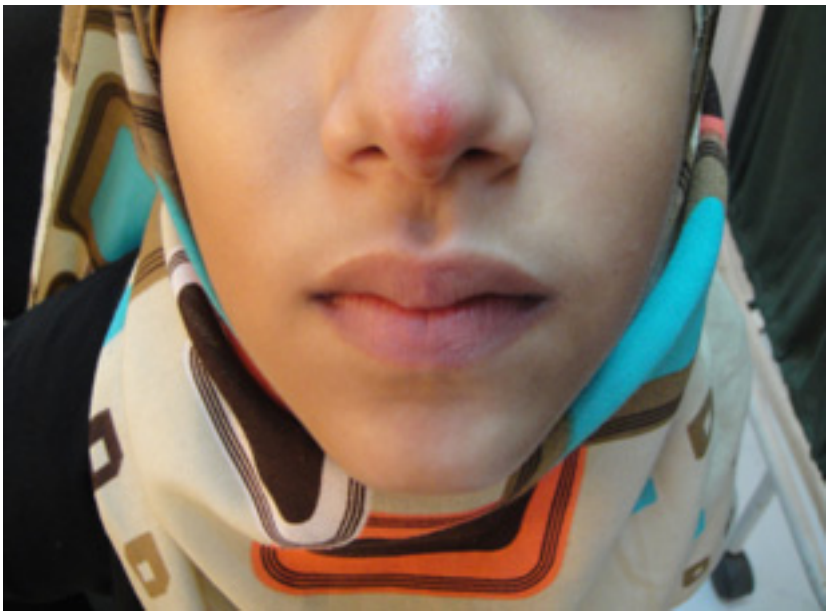


Figure 5: Ulcerated on lower limb

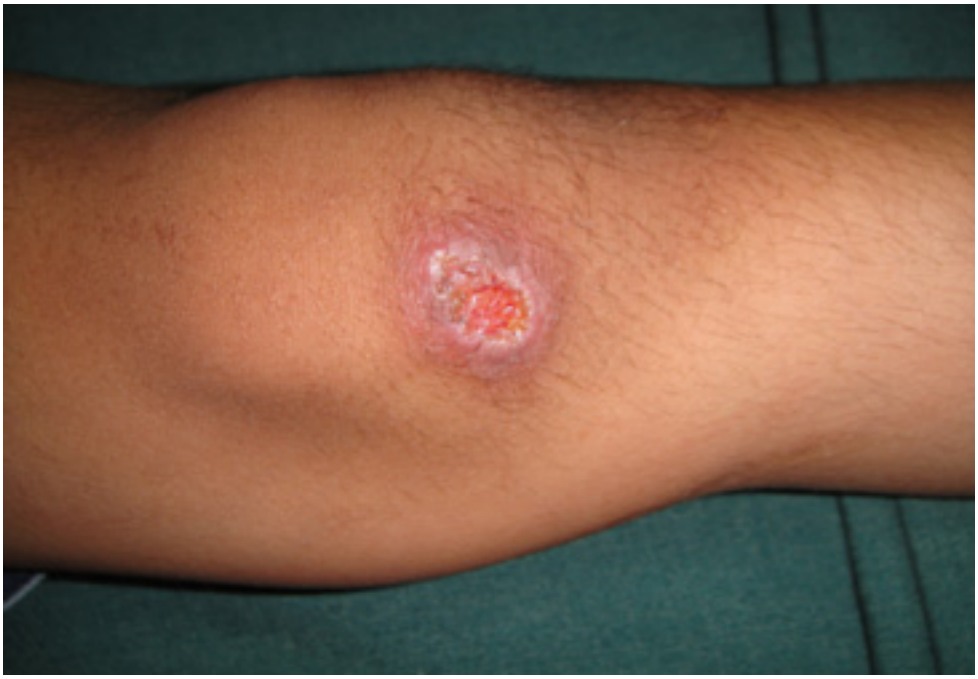


Figure 6: Multiple lesions on upper limb

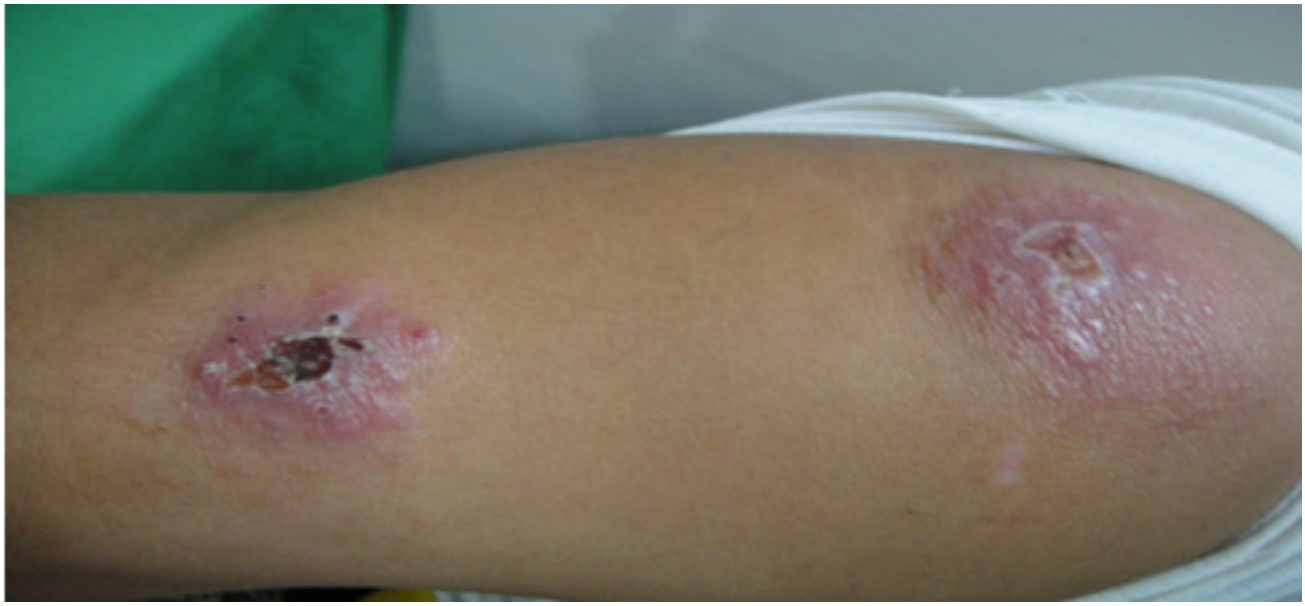


Table 2 reveals the distribution of sex among the study patients in which males and females of age group less than 20 years were predominant 38 (31.1%) and 18 (14.8%) respectively. The rest of the patients, males and females, were convergent. The difference between values was not statistically significant.

Table 2: Distribution of sex related to age groups

Sex / Age	Males		Females		Total	
	No	(%)	No	(%)	No	(%)
< 20	38	(31.1%)	18	(14.8%)	56	(45.9%)
20-39	17	(13.9%)	14	(11.5%)	31	(25.4%)
≥ 40	18	(14.8%)	17	(13.9%)	35	(28.7%)
Total	73	(59.8%)	49	(40.2%)	122	(100%)

Calculation of percentage out of the total patients 122

P > 0.05

In Table 3 most of the lesions' sites were lower limb 63 (51.6%) followed by upper limb 37 (30.5%) and face (9.0%). The single lesions were predominant 76 (62.3%) while multiple lesions were 46 (37.7%). The majority of lesion sizes were 0.5 cm 67 (54.9%) and 1 cm 50 (41%). Skin smear was positive in 102 (83.6%), negative in 9 (7.4%) and not done in 11 (9.0%) patients.

Table 3: Characteristics of cutaneous lesions among study patients (n = 122)

Variables	No	%
Site of lesion:		
- Lower limb	63	51.6
- Upper limb	37	30.5
- Face	11	9.0
- Upper & lower limb	3	2.5
- Both lips	2	1.6
- Face &lower limb	2	1.6
- Face & upper limb	2	1.6
- Nose	2	1.6
Number of lesions:		
- Single	76	62.3
- Multiple	46	37.7
Size:		
0.5 centimeter	67	54.9
1 centimeter	50	41.0
0.75 centimeter	3	2.5
1.5 centimeter	2	1.6
Skin smear:		
- Positive	102	83.6
- Negative	9	7.4
- Not done	11	9.0

Discussion

Leishmaniasis is a worldwide disease (7,8,9). The World Health Organization (WHO) estimates approximately 1 to 2 million new cases of leishmaniasis each year, all over the world (7,10). Twenty Leishmania species are pathogenic for humans and 30 sand-fly species are proven vectors (8). There are two main epidemiological entities (8); zoonotic: where animal reservoir hosts are involved in the transmission cycle and Anthroponotic: where man is the sole reservoir and only source of infection for the vector (8,11,12).

In the present study we found 122 patients were diagnosed with cutaneous leishmaniasis and males were significantly more affected than females; they were 73 (59.8%) males and 49 (40.2%) females with the ratio male to female 1.5:1. However, in a study that was conducted in southeastern France (13), males and females were equally affected with cutaneous leishmaniasis. Other studies in North-central province of Sri Lanka (14), in Lorestan, Iran (15) and Al-Badarna, Libya (16) have shown similar findings to our results.

This sex difference can be attributed to the following: a) most of the residents of Wadi Hadramout are farmers working on farms and they are at risk of sandfly bites. Males are more active in the palm plantations and harvesting dates, they are more prone to sandfly bites.

In our study the age of patients ranged between 1 to 62 years. The mean age of the patients is 26.5 ± 18.1 years and the highest numbers of patients 56 (45.9%) were less than 20 years of age, which is similar to that reported by others (17,18).

In contrast, Sharma et al (19) found a higher incidence of cutaneous leishmaniasis in persons 21-30 years of age. As age increased, the number of patients decreased; this finding may be caused by acquired immunity.

The present study found that most lesions' sites were lower limb 63 (51.6%) followed by upper limb 37 (30.5%) and face (9.0%). Similar findings were reported by Syed et al (20) from Pakistan that 75% of the patients had lesions on the legs and feet.

The study results of Khatri et al (21) from northwestern Yemen varied to our findings. They reported that the lesions were located on the face in 120 (88%) patients, upper extremities in 31 (23%), lower extremities in 17 (12.5%) and neck in one patient. Also, Al-Qubati (22) mentioned that most lesions occur in the head region, most commonly nose, cheeks, and lips, with about 30% noted on the extremities and a few on the trunk.

Aara et al (17) from India mentioned that the most lesions were located on exposed parts of the body such as the face (33%), upper extremities (41%), and lower extremities (20%).The trunk was involved in only 2% of patients.

Al-Nahhas et al (23) from Syria mentioned that the lesions were mainly located on the upper extremities (67.5%) compared with 25.9% on the facial region and 6.5% on the legs, typical exposed fly bites areas.

This variation of CL lesions location may be due to the exposure of these two sites to the environments more than the other site of the body and to the direct contact with animals and soil because of the traditional clothes of males in Valley Hadramout, which make the lower limbs uncovered.

The majority of lesion sizes in our study were 0.5 cm 67 (54.9%) and 1 cm 50 (41%) which is smaller than that reported in a previous study in northwestern Yemen which reported that the size of the lesions varied from 0.5 to 8 cm (21).

Also, it was smaller than that reported by Aara et al (17) that Lesions varied in size from a few millimeters to 12 cm in diameter and they found a total of 1,938 (71%) of 2,730 lesions ranged in size between 0.5 cm and 3.0 cm, and only 48 lesions were > 5.0 cm.

Similar to our finding was that reported by Aguado et al (24) from Spain that the most common lesion size in their study was 0.5 cm followed by 1 cm.

In our study the single lesions were predominant 76 (62.3) while multiple lesions were 46 (37.7%), similar to the results found by Khatri et al (21) in which eighty-seven (64%) patients had a single lesion, and the rest had multiple lesions. Also, a study finding from Iran reported that the number of lesions was one lesion in (67.7%) of the patients and (32.3%) multiple lesions (15).

Khatri et al (21) mentioned that the types of lesion were: nodulo-ulcerative, 75 (55%); ulcerated plaques, 31 (23%); plaques, 19 (14%); nodular, 5; papular, 2; diffuse infiltration, diffuse infiltration with ulceration, and verrucous thick plaques, 1 each.

The results of the current study revealed that the most common type of lesions were nodulo-ulcerated 52 (42.7%) followed by nodular 45 (36.9%), papulo-nodular 17(13.8%), plaque 5(4.1%) and ulcerated lesions 3(2.5%).

To some extent the results were consistent with previous studies from northwestern Yemen (21) and from Turkey (25). Skin smears were positive in 102 (83.6%), negative in 9 (7.4%) and not done in 11 (9.0%) patients.

Conclusion

We carried out this study in an attempt to compile cutaneous leishmania frequency, types and site locations in patients who attended to Seiyun hospital.

Males were more than females.

The results illustrated that male and female patients of the age less than 20 years are predominant. The most common types of lesions were nodulo-ulcerated followed by nodular and the most of lesions' sites were lower limb followed by upper limb. The single lesions were predominant and the majority of lesion sizes were 0.5 cm. We concluded that Wadi Hadramout is an endemic region of cutaneous leishmania.

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Obesity Management in Primary Health Care

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ABSTRACT

Obesity is a key public health problem across the world. Easy solutions are unlikely, given the complex interaction between the abundant availability of energy dense food, and the ever decreasing demand for energy expenditure in the modern world. This review paper addresses the issues of overweight and obesity in primary health care.

Key words: obesity, primary health care, management

Introduction

Obesity is a key public health problem across the world. It is a persistent state that is multi-factorial in origin, intricate to treat, and is a key contributor to multiple diseases including heart disease, type II diabetes, hypertension, stroke and some cancers. Simple solutions are improbable knowing the multi-faceted interaction between the copious accessibility of energy dense food, the yet decreasing demand for energy expenditure in the modern world, and the effect of our genetic make up (1, 2). Many physicians do not tackle the question of overweight and obesity with their patients who fulfill the criteria for obesity or overweight, or with persons that are at risk of becoming obese (3,4).

Management of Obesity

Systemic management of overweight and obesity is the key for successful approach. It is important to pinpoint patients who would benefit from nutritional counseling, since the behaviors that increase a patient's risk for related morbidity and mortality are seldom what bring a patient to the office. A detailed physical activity and nutrition history is a critical step in helping overweight and obese patients identify and implement healthier behaviors. Primary care physicians should follow the steps below:

Ask Is the patient ready to make a change?

As frequently as is appropriate, family physicians should ask every patient who is at risk for overweight whether he or she is willing to make one or more health behavior changes.

Advise

There is at least value in simply notifying a patient that his or her BMI is harmful. For patients who express an interest in making one or more changes, advice about nutrition and physical activity must be clear, exact and geared tailored to the patient's lifestyle, experience and capabilities.

Assess BMI

The first step in assessing the overweight of the patient is calculating the BMI. BMI is similar to blood pressure as a vital sign. It must be used to establish health risks and to direct discussion with patients about health behavior changes.

A BMI of 25.0 to 29.9 kg per m2 is defined as overweight; a BMI of 30.0 kg per m2 or more is defined as obesity.

Waist Circumference

Waist circumference, is an significant independent risk factor for cardiovascular disease, type 2 diabetes, dyslipidemia and hypertension (5,6). The waist measurement must be taken around the smallest area below the rib cage and above the umbilicus.

Waist circumference measurements greater than 40 inches (102 cm) in men or 35 inches (89 cm) in women indicate an increased risk of obesity-related comorbidities.

Metabolic Syndrome

The metabolic syndrome consist of five criteria, three of which must be present to make the diagnosis (7,8).

Table 1 lists these criteria.

Telling a patient that he or she has the metabolic syndrome may create a precious counseling chance.

Health Implications

There is little support from prospective studies revealing that weight loss by obese individuals ameliorate long-term morbidity and mortality, strong evidence insinuates that obesity is linked to increased morbidity and mortality and that weight loss in obese persons reduces important disease risk factors (9,10).

In adults, elevated disease risk increases separately with increasing BMI and excess abdominal fat.

Cardiovascular and other obesity-related disease risks increase markedly when BMI exceeds 25.0 kg per m2. Overall mortality starts to increase with BMI levels greater than 25 kg per m2 and increases most considerably as BMI levels surpass 30 kg per m2. Waist circumference measurements greater than 40 inches (102 cm) in men and 35 inches (89 cm) in women also point to an increased risk of obesity-related comorbidities (9).

Table 1: NCEP ATP III Diagnostic Factors for the Metabolic Syndrome*

Risk Factor Defining Level
1. Abdominal obesity Men: >102 cm (40 inches)
(waist circumference) Women: >88 cm (35 inches)
2. Triglycerides >150 mg per dL (1.69 mmol per L)
3. High-density lipoprotein Men: <40 mg per dL (1.04 mmol per L)
(HDL) cholesterol Women: <50 mg per dL (1.29 mmol per L)
4. Blood pressure >130/85 mmHg
5. Fasting glucose >110 mg per dL (6.1 mmol per L)
*Diagnosis is established when three or more of these risk factors are present.

Management

There is discord concerning whether the known dangers of being obese cause a greater health risk than the possible hazards of treatment(9,11,12). It is preferable to treat patients with a BMI of 25.0 to 29.9 kg per m^2 or a high waist circumference, and two or more risk factors. Treatment is also preferable for patients with a BMI of 30 or more kg per m2 regardless of risk factors. Successful management embraces dietary therapy, physical activity, behavior therapy, pharmacotherapy and amalgamation of these methods (9). Drugs must be used as a part of a comprehensive plan. Currently, an appetite suppressant, sibutramine (Meridia), and a lipase inhibitor, orlistat (Xenical), are labeled by the U.S. Food and Drug Administration for long-term use and may be helpful in the treatment of suitable high-risk patients.

Pharmacotherapy is used in patients with a BMI of 30 or more kg per m2 and no associated obesity-related risk factors or diseases, or patients with a BMI of 27 or more kg per m2 with associated obesity-related risk factors or diseases (i.e., hypertension, dyslipidemia, coronary heart disease, type 2 diabetes [formerly noninsulin-dependent diabetes] and sleep apnea).

Surgery may be entertained for difficult cases where the patients do not respond to medical treatment because such individuals are at high risk for the comorbidities associated with obesity. Surgical treatment of clinically severe obesity normally is done to restrict caloric intake (e.g., vertical banded gastroplasty) or to combine caloric restriction with some degree of malabsorption (e.g., Roux-en-Y gastric bypass, biliopancreatic bypass).

Special Consideration in Children

Currently children normally eat more calories than they burn up in physical activity. This discrepancy results from several recent alterations at home, school, and neighborhood environments. The Institute of Medicine (IOM) study, Food Marketing to Children and Youth: Threat or Opportunity (13) gives a scary report of how this influences children's health. Food marketing, the IOM says, deliberately targets children who are too young to differentiate advertising from genuineness and leads them to eat high-calorie, low-nutrient "junk" foods; companies succeed so well in this endeavor that business-as-usual must not be allowed to persist.

The IOM report gives enough evidence to maintain extra policy actions. Restrictions or bans on the use of cartoon characters, celebrity endorsements, health claims on food packages, stealth marketing, and marketing in schools, along with federal actions that promote media literacy, better school meals, and consumption of fruits and vegetables.

In the pediatric patients clinical evaluation must include determination of the BMI percentile (for age and sex) and vigilant assessment to pinpoint potential complications of obesity such as hypertension, dyslipidemias, orthopedic disorders, sleep disorders, gallbladder disease and insulin resistance (14). Treatment must be considered in children with a BMI higher than the 85th percentile and complications of obesity, or a BMI higher than the 95th percentile with or without complications.

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