REVIEW ARTICLE

SYDROME X: Time to pay heed!

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The terms overweight, diabetes mellitus and high blood pressure are becoming common norms of any health conscious society in the world. There is a worldwide increase in all these variables in mostly all nations of the world. It is common knowledge that anyone who is overweight or obese, as we call it in our medical terminology, will land up eventually with increasing age into one or more of its associated diseases or might end up with its complications, like unhealthy lipid levels or heart diseases. Also, such abnormalities run in families suggesting a genetic tendency; such individuals are then more at risk of developing them. These observations are factual and reflect the trends of societies across the world.

It has been believed for years that being overweight, developing diabetes mellitus and hyperlipidemias leading inevitably to high blood pressure are independent entities having different pathogenesis. However, ongoing researches point to a contradictory perspective that suggests that this is not the case. These varieties of abnormalities are part and parcel of a single pathology developing in the body having a common pathogenesis. This has been called by a lot of different names like the Insulin resistance syndrome/Syndrome X/Metabolic syndrome/ Dysmetabolic syndrome.[1] For a decade or more, the existence of such a syndrome has been suggested on the basis of innumerable studies done world over. Ongoing researches both in the developed and the developing nations do point to such a scenario.

These consortiums of abnormalities, now the Metabolic Syndrome, were thought to be diseases of old age coming up at a later part of life not relevant to the younger generation. New facts suggest a totally opposite observation: these are no longer diseases of later life or diseases of grandparents or parents but are becoming evident in a far younger age group. This age group until now has been considered fit and healthy. In addition, mounting evidence indicates an increased tendency of this syndrome in the age group starting from as young as 18 years and beyond!

The story does not end here. Such a diagnosis if made actually predicts the development of complications of systemic origin developing due to atherogenic plaque deposition. In addition to being associated with afore mentioned characteristics, it is seen that there is an increased likelihood in diagnosed individuals of pro-thrombotic (blood clotting) and pro-inflammatory diseases. It foretells increased tendency towards cardiovascular diseases (CVD) like ischemic heart disease, cerebrovascular accidents and end organ damage, for example, renal diseases to name a few. Current studies suggest that such a predisposition can be diagnosed in an age group[2] starting from as young as 18 years with a view to prevent and even treat it where necessary.

Using WHO and NCEP ATP III (Adult Treatment Panel: third report of the NCEP expert panel on Detection, Evaluation and Treatment of High Blood Cholestrol in Adults), Metabolic Syndrome is defined in patients having three or more of the following:

- Central obesity as measured by the waist circumference (males greater than 40 inches; females greater than 35 inches)
- Fasting triglycerides greater than or equal to 150 mg/dL (1.69 mmol/L)
- HDL-cholesterol [males: less than 40 mg/dL (1.04 mmol/L); females: less than 50 mg/dL (1.29 mmol/L)]
- Blood pressure greater than or equal to130/85 mm Hg
- Fasting glucose greater than or equal to 110 mg/dL (6.1mmol/L)[3, 11]

Comparing prevalence studies in various parts of the world gives interesting results: United States of America shows a statistical prevalence of 21-24 % [3]; Italians have a prevalence of 22% [3]; Omanis give a prevalence of 21% [4] and a Turkish study quotes the same as 33% [5] in the adult population over 19 years of age. Such is the case in age groups starting from 18 years going to 80-90 years. With categorization based on age grouping, it is seen that incidence in the population increases with an increase in age starting from 3-4% in the younger group going up till 25% in the elderly [3,4,5]. Taking into consideration gender specification, this disease is rifer in females than males [3, 4, 5]. Females show greater abnormalities in most of the criteria used in the diagnosis of metabolic syndrome, especially obesity, hypertension and dyslipidemias. Also, associated conditions in females like the Poly Cystic Ovarian Disease [11] predispose them to a greater incidence of insulin resistance and its accompanying abnormalities.

Hence, no nation in the world is exempt from the effects of this metabolic abnormality which weighs down on its public health resources. Developing into a chronic ailment with innumerable complications, the costs of all the investigations and

the treatment are high. Hence, all effected nations, especially those with limited resources, should undertake programs for prevention, early detection and early treatment to cut down the expenses as much as possible. Pakistan has no available data regarding frequency and prevalence of syndrome X carried out on such a vast population. The need of the hour is to undertake such studies in view of getting the true impact of this syndrome on our population so that further steps can be taken to deal with its consequences. More emphasis should be on preventive programs based on alterations of modifiable risk factors and early detection of the disease in predisposed/high risk individuals. Utilization of inexpensive and low cost tests to identify such people in a younger age group is one of the many ways to implement cost reduction on individual and public health resources.

Obesity is becoming rampant worldwide, so much so that it is now taking the shape of an epidemic [3-6]. To make things worse, being overweight is becoming far more common in a very young age group starting from early childhood, through adolescence and not sparing the middle aged and the elderly. Pediatric obesity is becoming more common, leading to the same in adolescents and young adults. Children in a younger age are taking unhealthy food, for example, preferring soft drinks over fresh juices, taking more meaty products as compared to fresh vegetables or pulses or taking refined products in place of natural/fiber rich ones.

To add to the already bleak scenario is a tendency towards not exercising and preferring inactivity over any sort of physical activity or sports[8]. An increase in body weight of nearly 1kg has been seen to increase the risk of developing metabolic syndrome as opposed to a decrease in 5-10% body weight improving symptomtology[9]. These habits tend to stick around and become permanent as the kids come of age and it becomes hard though not impossible to adopt a change in dietary habits. Such a lifestyle breeds overweight youngsters who grow into overweight adults with an ever increasing tendency to develop the complications of obesity.

The definition of obesity has been described by the ATP III (Adult Treatment Panel: third report of the NCEP expert panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults) [10]. It has been suggested by various studies that visceral /android obesity is of more importance than somatic obesity. Former describes deposition of excess fat in the abdominal area and abdominal organs. Various methods have been proposed and tested to measure it; anthropometric measurements include the waist circumference (WC), waist-hip ratio (WHR), body mass index (BMI). A variety of imaging techniques, for example, dual energy x-ray absorptiometry and computed tomography (CT scan) yield equally good results and each enhances credibility of the other [6, 7].

As more and more of obesity and its associated abnormalities are being studied the adipose tissue is being understood better than before. In the light of these, additional roles are being assigned to white adipose tissue which is now recognized as an active endocrine and paracrine gland, immune modulator, inflammatory regulator and regulator of lipoprotein and glucose metabolism. It synthesizes and elaborates adipocytokines[11], a variety of chemical mediators, hormones, cytokines and immune modulators, having as much variety of functions. Evidence in numerous studies links fatty tissue to its myriad of effects. A few examples of these adipocytokines are leptin, adiponectin, IL-6 (interleukin), TNF-α (tumour necrosis factor) and CRP (C-reactive protein) [11, 12] PAI-1 (plasminogen-activator inhibitor) and resistin naming a few[13].

This anthology of metabolic abnormalities, as has been mentioned before, is called by a variety of names. One of these is the insulin resistance syndrome. It is so called as this is one of the main anomalies that underlie the pathological changes seen in such patients. In essence, insulin resistance develops far before the development of overt diabetes mellitus or the co-morbid factors [14]. The pancreas responds to normalize this abnormality with secretion of more and more insulin. Therefore, insulin resistant individuals at this stage of their disease have higher plasma levels of insulin (hyperinsulinemia), this being the initial step in the pathogenesis of type 2 diabetes mellitus[15]. This hyperinsulinemia maintains normal glucose levels till the exhaustion of the pancreatic beta cells due to over activity. The ensuing step then is an impaired early secretion of insulin leading initially to postprandial (after meals) hyperglycemia and then fasting hyperglycemia when a diagnosis of the disease is made [14, 15]. This advanced stage of the disease when glucose appears in the urine and high levels are present in the plasma is easy to diagnose; it is the initial stages of insulin resistance which are difficult to catch.

Insulin resistance, as was previously thought does not essentially come with increase in age. As discussed earlier, with obesity becoming more rampant in a young age group worldwide, incidence of diabetes mellitus type 2 also is catching up. As more and more adolescents are putting on unnecessary pounds, resistance to insulin is increasing as is evident in various studies abroad [16]. Our society is blindly following these western trends, so the situation here would be no different in the near future. The need of the hour in any society,

developed or developing, is to focus not only on how to prevent or manage the disease and its attendant complications but also when to start prevention [17]. The disease is showing an early tendency to develop, so logically prevention should also start early.

Disturbed glucose and insulin metabolism strongly relate to all other components of the syndrome. The link between obesity and these two has been adequately addressed; metabolic disturbances leading to dyslipidemia, hypertension and atherosclerosis which are the cause for cardiovascular disease morbidity and mortality remain to be discussed. Insulin has a major role to play in determining not only glucose metabolism but also influences lipid metabolism of the body. So strong is this influence on lipid profile that diabetes mellitus has been called "more a disease of lipids than carbohydrate metabolism[18]." It promotes the deposition of triglycerides in lipid stores of the body by quite a number of mechanisms[19]. In diabetes mellitus, these controlling mechanisms become disturbed due to resistance/deficiency of insulin and in uncontrolled disease, these mechanisms cause an increase in the plasma levels of triglycerides, chylomicrons and free fatty acids (FFA) making the plasma lipemic[18]. In addition to these typical lipids being raised in plasma, insulin resistance also causes appearance of smaller and denser low density lipoprotein particles and enhanced post prandial accumulation of remnant lipoproteins; changes leading to enhanced cardiovascular disease risk[20]. Easy and abundant availability of these varieties of "bad cholesterol" in a backdrop of adiposity provides the required cytokines necessary for plaque deposition. Adiposity, as was previously mentioned is correlated with altered production of adipocytokines and inflammatory mediators which are the source of angiopathy and vascular damage [20, 21]. Atherosclerosis results, which in diabetics is more marked in the microvasculature. Cardiovascular disease (CVD) as this is called effects the coronaries, cerebral vessels and the peripheral vessels. It is the greatest cause for concern in diabetics as this eventually ends up with angina, myocardial infarction, stroke and myriad end organ diseases. The incidence of these outcomes is twice as marked in diabetics as in the non-diabetics [22].

Additionally, evidence linking this scenario of abnormal lipid profile with newly found enzymes helps to put in at least some missing pieces of the puzzle. An endothelial derived lipase has been shown to influence high density lipoprotein metabolism (HDL) in animal models [23]. Endothelial lipase (EL) as it is called belongs to the triacylglycerol (TG) lipase family as do the other lipases, namely, lipoprotein lipase (LPL) and hepatic lipase (HL). Both of these influence high density lipoprotein metabolism but endothelial lipase is the only lipase synthesized and expressed by the endothelial cells, hence its name. Over expression of the enzyme is associated with:

- deterioration of lipid profile
- elevated plasma triglycerides
- elevated apolipoprotein B concentrations and smaller low density lipoprotein size
- elevated proinflammatory cytokine concentration [24]

Increasing research now suggests the same pathophysiology in humans with strong correlations being found between increased endothelial lipase activity and proinflammatory diseases like the metabolic syndrome [24, 25, 26] as well as subclinical atherosclerosis.

Going back to the criteria defining the metabolic syndrome, hypertension being one of them, the link between the former and insulin resistance is a hot topic of debate among medical specialists. Numerous theories as to the cause of hypertension have been proposed. Some believe endothelial dysfunction to be the link between insulin resistance and development of hypertension. Studies indicating vascular sensitivity to insulin show the endothelium to be directly responsive to insulin by vasodilatation which is mediated by release of nitric oxide from endothelial cells. Both obese non-diabetic and diabetic individuals have been shown to have impaired endothelial function and impaired response to haemodynamic actions of insulin [27, 28]. What is more, this impairment of endothelium predisposes to macro- and micro-vascular complications leading to cardiovascular thrombotic disease and its inherent defects like enhanced leucocytic adhesion, thrombosis and smooth muscle cell proliferation in the arterial wall.

Others blame yet different events in the relationship between high blood pressure and metabolic syndrome. An increased activity of the sympathetic nervous system, increased angiotensin II levels, hyperuricemia coupled with salt sensitivity contributes to increased likelihood of these individuals developing essential hypertension [20, 28, 29]. Angiotensin II contributes to the development and progression of cardiovascular and renal end points as angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors demonstrate a protective effect [29]. In experimental hyperuricemia, the development of preglomerular arteriolar lesions lead to resultant reduced renal blood flow and hypertension, and both haemodynamic changes and arteriolar lesions do not occur if hyperuricemia is prevented with allopurinol. The mechanism appears to be mediated by direct entry of uric acid into both endothelial and vascular smooth muscle cells,

resulting in local inhibition of endothelial nitric oxide levels, stimulation of vascular smooth muscle proliferation and of vasoactive and inflammatory mediators [28]. Hence, hyperuricemia is considered a major risk factor among many in the development and further progression of high blood pressure. Since metabolic syndrome associated hypertension is also associated with hyperuricemia as well as obesity, all these clues fit into the picture to complete to some extent the pathogenetic link.

A lot is associated with the hypertension of insulin resistance syndrome. The high blood pressure readings encompass folks of all age groups: it is seen in children as young as 6-10 years of age[30] becoming more common as age increases. Statistical studies indicate hypertension and type 2 diabetes mellitus have a reciprocal relationship; individuals with hypertension are more likely to develop type 2 diabetes and type 2 diabetics are twice at risk of developing the former. Additional data indicate a 75% increase in cardiovascular disease complications in diabetics due to HPT which means that such patients require intense treatment and monitoring of both their glucose and blood pressure levels [31].

CONCLUSION

To sum up, Pakistan is gaining on the prevalence of metabolic syndrome and the need of the present times is to pay attention and implement programs at all stages of the disease. The existing and the upcoming cases require careful monitoring of all parameters of the syndrome to prevent and treat it at initial stages when complications have not made the scenario drab.

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