Metabolic Syndrome X is Common in Indians: But, Why and How?

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Abstract

Metabolic syndrome X is common in Indians. But the exact cause for this is not clear. Earlier, I proposed that this could be due to low activities of $\Delta^6$ and $\Delta^5$ desaturases and consequent decreased plasma and tissue concentrations of long-chain polyunsaturated fatty acids of $\omega$-6 and $\omega$-3 series since perinatal period. This implies that perinatal to adult life supplementation of long-chain polyunsaturated fatty acids could prevent, arrest or postpone the development of metabolic syndrome X and its complications.

WHY AND HOW ABDOMINAL OBESITY OCCURS?

Abdominal obesity, atherosclerosis, insulin resistance and hyperinsulinemia, hyperlipidemias, essential hypertension, type 2 diabetes mellitus, and coronary heart disease (CHD) are the major components of metabolic syndrome X. Certain other features of metabolic syndrome X also include: hyperfibrinogenemia, increased plasminogen activator inhibitor-1 (PAI-1), low tissue plasminogen activator, nephropathy, micro-albuminuria, and hyperuricemia (reviewed in 1). Several studies showed a high incidence of various features of metabolic syndrome X in Indians compared to the Western population.1,2 The exact cause for this is not known. It is generally believed that a high incidence of abdominal obesity and insulin resistance in Indians could be responsible for the higher prevalence of metabolic syndrome X seen in them. Although genetics could play an important role in the higher prevalence of metabolic syndrome X in Indians, it is not yet clear as to how the so-called genetic factors interact with environmental and dietary factors and if so, how such an interaction(s) reflects in the onset of metabolic syndrome X. Further, the incidence of abdominal obesity and insulin resistance is common in Indians but, it is not clear why they should occur frequently in them. If a reasonable cause and/or the aetiological factors responsible for abdominal obesity and insulin resistance are identified, it is expected to lead to both preventive and curative measures.

RISK FACTORS IN INDIANS

The established risk factors that might predispose Indians to develop various components of metabolic syndrome X include: abdominal obesity, high prevalence of type 2 diabetes, hypertension, low concentrations of high-density lipoprotein (HDL) cholesterol, hypertriglyceridemia, hypercholesterolemia, and sedentary lifestyle. Insulin resistance is common in all these conditions. Hyperinsulinemia may be a consequence of this. It should be noted that insulin resistance may not always be present in these conditions and even when present it may not occur in all tissues of the body at the same time. For instance, in the early stages of metabolic syndrome X insulin resistance in muscle tissue is common whereas adipose tissue is not resistant to insulin.3 This may explain why exercise is beneficial in the prevention and treatment of insulin resistance since, it enhances glucose utilization in the muscles. By decreasing insulin resistance, exercise halts the progression of metabolic syndrome X at least temporarily.
higher lipoprotein lipase (LPL) activity. Females have the unique ability to protect visceral depots from fat accumulation up to a certain degree of obesity whereas in males deposition of excess fat in this region parallel with other depots. This difference in the distribution of fat is attributed to the action of female sex steroid hormones on the regulation of adipocyte metabolism in concert with cortisol, which has a regulatory role on LPL. Omental adipose tissue contains almost four times the number of glucocorticoid receptors (GR) as subcutaneous adipose tissue with similar Kd values. LPL activity in subcutaneous adipose tissue was approximately two to four folds lower compared to omental adipose tissue. But no correlation was found between GR number and LPL activity when each depot was investigated separately. However, a positive correlation between LPL activity and glucocorticoid binding was noted. Human adipose tissue dexamethasone (glucocorticoid) binding was higher in omental than in subcutaneous adipose tissue, whereas LPL activity was higher in omental than in subcutaneous adipose tissue in both men and women. These results suggest that there are distinct differences between different depots of fat in their response to glucocorticoids and display wide differences in their biochemical properties. Furthermore, the gluteal region fat cells from females had higher insulin receptor binding and higher rates of non-insulin-stimulated and maximally insulin-stimulated rates of glucose transport and glucose metabolism and leptin mRNA is markedly overexpressed in abdominal subcutaneous adipocytes compared with omental adipocytes. A significant inverse correlation exists between adipocytes, PPAR-γ expression and BMI. Cellular inhibitor of apoptosis protein-2 (cIAP-2) mRNA was expressed at higher levels in omental than subcutaneous adipocytes. CIAP-2 is involved in the regulation of tumour necrosis factor-α (TNF-α) signaling that raises the possibility that depot-specific differences exist in the regulation of adipocyte apoptosis. We found that subcutaneous adipose tissue produces less interleukin-6 (IL-6) and corticosterone and more TNF-α in comparison to mesenteric adipose tissue. Since PPAR-γ is involved in adipocyte development and insulin sensitivity and has a negative control on TNF-α synthesis indicating the existence of a complex but local network of events in the regulation of adipocytes accumulation, metabolism and function.

The biochemical and functional differences between different depots of adipose tissue suggests that this may have relevance to their role in metabolic syndrome X. It is likely that abdominal adipose tissue is distinctly different both biochemically and physiologically compared to the subcutaneous adipose tissue. Mice overexpressing 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) enzyme selectively in adipose tissue develop abdominal obesity and exhibit insulin-resistant diabetes, hyperlipidemia, and hyperphagia despite hyperleptinemia. These features are similar to those seen in Indians with metabolic syndrome X. This suggests that abdominal obesity is like localized Cushing’s syndrome. Earlier, I suggested that the activity of 11β-HSD-1 in the abdominal adipose tissue of Indians could be higher compared to European whites. It is also likely that the activity of 11β-HSD-1 (and so the levels of its product corticosterone) is high in the abdominal adipose tissue compared to that seen in the subcutaneous adipose tissue that may explain why abdominal obesity is common in Indians. In view of this, it is important to know the factors that regulate the activity of 11β-HSD-1 in adipose tissue. Such an understanding may lead to develop strategies to prevent or treat abdominal obesity effectively.

Metabolic Syndrome X as a Low Grade Systemic Inflammatory Condition

Obesity

There is reasonable evidence to suggest that low-grade systemic inflammation plays a significant role in the pathobiology of metabolic syndrome X. Plasma levels of C-reactive protein (CRP), TNF-α, and IL-6 that are markers of inflammation, are elevated in subjects with obesity, insulin resistance, essential hypertension, type 2 diabetes, and CHD both before and after the onset of these diseases. A positive association between BMI and CRP was observed in otherwise healthy adults. An increase in CRP concentration in overweight children compared with normal weight children was also reported. Elevated CRP concentrations have been associated with increase in risk of CHD, ischemic stroke, peripheral arterial disease, and ischemic heart disease mortality in healthy men and women. It was observed that higher adiposity indicates higher CRP levels in children and adults. A strong relation between elevated CRP levels and cardiovascular risk factors, fibrinogen, and HDL cholesterol has been noted, suggesting a role for inflammation throughout life in the development of atherosclerosis and cardiovascular disease.

The elevated CRP concentrations are due to the increased expression of IL-6 in adipose tissue and its release into the circulation. IL-6 is a pro-inflammatory cytokine that stimulates the production of CRP in the liver. Higher adipose tissue content of IL-6 has been associated with higher serum CRP levels in obese subjects. In transgenic mice IL-6 is absolutely required for the induced expression of CRP. In overweight and obese subjects, serum levels of TNF-α were significantly higher than those in lean subjects. Weight reduction or moderate intensity regular exercise decreases the serum concentrations of TNF-α. Plasma TNF-α was negatively correlated with HDL cholesterol, glycosylated hemoglobin, and serum insulin concentrations reviewed in 11. Thus, in otherwise healthy but overweight and obese subjects elevated plasma/serum concentrations of CRP, IL-6 and TNF-α occur. A similar scenario seems to exist in insulin resistance, hypertension, type 2 diabetes mellitus, CHD, and peripheral vascular disease.

Insulin resistance and type 2 diabetes mellitus

Obesity is commonly associated with type 2 diabetes mellitus. Studies showed that subjects with elevated CRP levels at baseline testing were almost two times more likely to
Thus, chronic systemic elevation of acute phase reactants such as CRP and inflammatory cytokines IL-6, and TNF-α occurs in patients with diabetes. Hyperglycemia induced the production of acute phase reactants from the adipose tissue.22 TNF-α plays a role in insulin resistance and type 2 diabetes mellitus.23 Thus, increase in the incidence of type 2 diabetes in the elderly could be linked to alterations in the homeostatic mechanisms that control TNF-α, IL-6, and CRP levels. Why there should be an elevation in the levels of these pro-inflammatory markers in subjects with type 2 diabetes? The stimulus seems to be hyperglycemia. Esposito et al24 observed that when plasma glucose levels were acutely raised in control and impaired glucose tolerance (IGT) subjects and maintained at 15 mmol/L for 5 hours while endogenous insulin secretion was blocked with octreotide, in control subjects plasma IL-6, TNF-α, and IL-18 levels rose but were much lower compared to those seen in IGT. In IGT subjects the fasting IL-6 and TNF-α levels were higher than those of control subjects, and the increase in plasma cytokines levels lasted longer compared to control subjects. This raise in plasma cytokine levels was completely abrogated by simultaneous administration of antioxidant glutathione, suggesting a role for an oxidative mechanism in increases in circulating cytokines concentrations induced by glucose. In this context, it is interesting to note that dietary glycemic load is significantly and positively associated with plasma CRP in healthy middle-aged women.25 This coupled with the observation that glucose challenge stimulates generation of reactive oxygen species by leukocytes in humans and decreases vitamin E levels suggests that oxidative mechanism and pro-inflammatory process may be a mechanism whereby a high intake of rapidly digested and absorbed carbohydrates increase the risk of insulin resistance and CHD. In fact, it has now been shown that any high calorie diet rich in carbohydrates, fats (especially saturated and trans-fats) or protein stimulate the production of reactive oxygen species and pro-inflammatory cytokines IL-6, TNF-α, and IL-18, and CRP.23 Both IL-6 and TNF-α activate NADPH oxidase and thus enhance the generation of reactive oxygen species.24 These studies imply that the increased free radical generation seen in insulin resistance and type 2 diabetes mellitus are due to enhanced generation of IL-6, TNF-α, and CRP that in turn enhance NADPH oxidase activity. This ultimately leads to increase in oxidative stress and target organ damage seen in diabetes.

It is known that superoxide anion, one of the free radicals, interacts with nitric oxide (NO) and rapidly inactivates it producing peroxynitrite radical. The increased superoxide production accounts for a significant proportion of the NO deficit seen in diabetes and consequent vascular dysfunction.25 This reduced eNO (endothelial nitric oxide) and increased free radical generation is seen not only in diabetes but also in other associated conditions such as insulin resistance, obesity, hypertension, and CHD.30-33 The reduced eNO generation could be due to enzymatic uncoupling of L-arginine oxidation, deficiency of L-arginine, increased plasma concentrations of asymmetrical dimethyl arginine, decreased concentrations of co-factors of NO synthesis tetrahydrobiopterin, folic acid, and vitamin C.34 Thus, increased superoxide anion production, decrease in eNO, enhanced levels of asymmetrical dimethyl arginine, intracellular deficiency of anti-oxidants, folic acid and tetrahydrobiopterin are some of the common features seen in obesity, insulin resistance, type 2 diabetes, hypertension, CHD, hyperlipidemia, and metabolic syndrome X. These common features may also explain why all these conditions are closely associated with each other and occur together in a given individual. Furthermore, a study of the interrelationships between CRP, the metabolic syndrome X, and incident cardiovascular events among 14,719 apparently healthy women who were followed up for an 8-year period for myocardial infarction, stroke, coronary revascularization, or cardiovascular death showed that CRP levels greater than 3.0 mg/L was significantly associated with increased incidence of these diseases.35 This prospective data suggests that measurement of CRP adds clinically important prognostic information to the metabolic syndrome X.

**ADIPONECTIN IN OBESITY, INSULIN RESISTANCE, TYPE 2 DIABETES, AND METABOLIC SYNDROME X**

Adiponectin is a 29-kDa-adipocyte protein that seems to have an important role in insulin resistance, type 2 diabetes mellitus, and lipodystrophy. Plasma adiponectin (also called ACRP 30) levels are decreased in obese and type 2 diabetic subjects. An inverse association has been described between plasma adiponectin levels and insulin resistance (ref. Kern et al Diabetes). Plasma adiponectin and adiponectin mRNA levels were significantly lower in obese subjects. When men and women with a BMI < 30kg/m² were compared, women had a two-fold higher percent body fat, yet their plasma adiponectin levels were 65% higher (8.6 ± 1.1 and 14.2 ± 1.6 µg/ml in men and women, respectively). Insulin-sensitive subjects had two-fold higher plasma levels of adiponectin. Although no correlation between plasma IL-6 and leptin and adiponectin levels was observed, a significant inverse correlation between plasma and adipose tissue adiponectin and TNF-α and TNF-α mRNA expression was noted. Subjects with highest levels of adiponectin mRNA expression secreted the lowest levels of TNF-α from their adipose tissue in vitro.36 These results indicate that adiponectin expression from adipose tissue is higher in lean subjects and women, and is associated with higher degrees of insulin sensitivity and lower TNF-α expression and levels. Adiponectin mRNA levels were decreased by TNF-α and IL-6.37 This inverse relationship between plasma levels of adiponectin and TNF-α and IL-6 and the cytokine-induced reduction in adiponectin mRNA level in vitro suggests that endogenous cytokines modulate insulin resistance by influencing adipose adipokine,
and adiponectin. Matsubara et al. observed that women with higher BMI, body fat mass, total cholesterol, triglycerides and low HDL cholesterol had lower plasma adiponectin levels and higher CRP. This reciprocal relationship between CRP and adiponectin both in the plasma and adipose tissue indicates that adiponectin has anti-inflammatory actions and in the presence of low-grade systemic inflammation (as evidenced by an increase in plasma CRP level), adiponectin levels tend to be low. CRP causes NF-κB activation leading to the induction of monocyte chemoattractant peptide (MCP-1), IL-6 and iNOS gene expression and activates vascular smooth muscle cells, and increases plasminogen activator inhibitor-1 expression, a marker of atherothrombosis. This suggests that CRP is pro-atherogenic whereas adiponectin is anti-atherogenic. Studies in Pima Indians showed that subjects with high plasma adiponectin levels are less likely to develop type 2 diabetes, and may in fact protect against its development. Weight loss induced by diet control and/or exercise in obese women reduced plasma IL-6, IL-18, and CRP while adiponectin levels increased significantly. Weight loss improves endothelial dysfunction, increases insulin sensitivity, decreases plasma IL-6 and TNF-α, increases plasma anti-inflammatory cytokine IL-4 and IL-10, and enhanced adiponectin levels. Thus, adiponectin seems to have the ability to stimulate eNO and decrease superoxide anion generation whereas CRP interferes with eNO generation and action. Based on this it is suggested that exercise is anti-inflammatory in nature that explains its beneficial actions in protecting against the development of metabolic syndrome X.

**Essential Hypertension**

Fernandez-Real et al. observed elevated circulating IL-6 levels in women with hypertension and insulin resistance in men. Significant graded relationship between blood pressure and levels of ICAM-1 (intercellular adhesion molecule-1) as well as IL-6 was noted in apparently healthy men. Increase in pulse pressure was found to be associated with elevated CRP among healthy US adults. In the Women’s Health Study, CRP was associated with age, BMI, systolic blood pressure, HDL, smoking, and hormone replacement therapy. These results suggest that plasma levels of CRP and IL-6 are elevated in insulin resistance and hypertension. In an earlier study, we showed that patients with uncontrolled essential hypertension have elevated plasma lipid peroxides and low NO, and their leukocytes generated significantly higher levels of superoxide anion, and RBC membranes contained low vitamin E and superoxide dismutase (SOD). These abnormalities reverted to normal following control of blood pressure. These findings have now been confirmed by many other studies. We also showed that angiotensin II is the stimulus for this increased generation of free radicals. Now it is known that angiotensin II activates NADPH oxidase by stimulating c-Src, EGF receptor transactivation, phosphatidylinositol-3-kinase, and Rac, a small molecular weight G protein, in smooth muscle cells. Angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers significantly increased adiponectin concentrations in patients with hypertension. This indicates that insulin resistance seen in patients with hypertension is due to low adiponectin levels. Thus, subjects with obesity, type 2 diabetes, and hypertension have low plasma adiponectin levels. Since, β-blockers, and calcium antagonists inhibit free radical generation similar to ACE inhibitors, it is likely that they also enhance adiponectin levels. A positive correlation exists between plasma adiponectin levels and insulin sensitivity, and HDL cholesterol, whereas a negative relationship is seen with BMI, insulin, free fatty acid, and triglycerides but not with blood pressure. This suggests that one of the main mechanisms of action of antihypertensive drugs especially of ACE inhibitors and angiotensin-II receptor blockers is to increase insulin sensitivity and enhance insulin action, suppress free radical generation and augment eNO generation that ultimately results in their beneficial actions.

It is evident from the preceding discussion that elevation in the concentrations of pro-inflammatory cytokines, CRP, and free radicals; and decrease in eNO, anti-oxidants, and adiponectin occurs in obesity, insulin resistance, type 2 diabetes mellitus, hypertension, CHD, and, possibly, in hyperlipidemia. Based on this, it is suggested that measurement of CRP, TNF-α, and IL-6 can be used as markers of future development of type 2 diabetes, hypertension, and CHD. All obese individuals do not develop hypertension, type 2 diabetes and CHD. It is likely that those who are obese but do not have hypertension, type 2 diabetes, hyperlipidemia, CHD, and other features of metabolic syndrome X will have normal levels of CRP, TNF-α, IL-6, eNO, IL-4, IL-10, and adiponectin in their plasma. On the other hand, lean subjects (BMI < 25) who have hypertension, type 2 diabetes, CHD, and hyperlipidemia alone or in combination are expected to have elevated levels of CRP, TNF-α, and IL-6, and decreased levels of plasma eNO, adiponectin, IL-4 and IL-10. Thus, measurement of CRP, TNF-α, IL-6, IL-4, IL-10, eNO, and adiponectin could be used as markers to predict, prevent and prognosticate the development of metabolic syndrome X.

**Low-Grade Systemic Inflammation in Indians**

Metabolic syndrome X is common in Indians especially type 2 diabetes mellitus. But, the exact cause for this high incidence has never been adequately explained. Although Indians as a race may have a higher risk to develop various features of metabolic syndrome X, what are these genetic factor(s) has never been elucidated. One suggestion that has been made is the thrifty gene hypothesis. It was postulated the existence of metabolically thrifty genes that permit efficient utilization of food leading to fat deposition and weight gain at times of food abundance making the gene-bearer better able to survive during times of famine. Examples of thrifty genes include insulin and leptin. Non-diabetic Nauruans and Arizona Pima Indians have postprandial levels of plasma...
insulin that are almost triple those of Europeans. These populations when given ample food, first develop obesity and then develop type 2 diabetes mellitus, a propensity that they exhibit more compared to Europeans. Experimental rats carrying genes predisposing them to type 2 diabetes mellitus and metabolic syndrome X also involves environmental and lifestyle risk factors in the form of high calorie intake and low exercise. How can hyperinsulinemia, hyperleptinemia, high calorie diet, and lack of or low exercise be explained in terms of the low-grade systemic inflammation seen in metabolic syndrome X?

Indians have higher CRP concentrations than do European whites.\(^5^0,6^0\) It is likely that Indians also have higher levels of TNF-\(\alpha\) and IL-6\(^6^9,1^1\) (because IL-6 induces CRP production, whereas TNF-\(\alpha\) stimulates IL-6 synthesis). Elevated plasma TNF-\(\alpha\) levels have been associated not only with obesity and insulin resistance but also with hypertriglyceridemia, glucose intolerance, and hyperleptinemia, and negatively correlated with HDL cholesterol\(^6^1-6^3\) suggesting that plasma levels of TNF-\(\alpha\) and in turn those of CRP and IL-6 are closely related to the biochemical parameters that are known risk factors for the development of metabolic syndrome X and type 2 diabetes mellitus. HDL stimulates endothelial nitric oxide (eNO) synthesis\(^6^4\) and NO in turn inhibits LDL oxidation.\(^6^5\) Both oxidized LDL and reduced levels of eNO enhance the risk of atherosclerosis and thrombosis. This may explain the high incidence of CHD in Indians, which is supported by our study in which it was observed that plasma lipid peroxides were increased and NO concentrations were low in Indians with type 2 diabetes, hypertension, and CHD.\(^6^6\) TNF-\(\alpha\) and IL-6 augment whereas insulin-like growth factor-I (IGF-I) and insulin suppress the activity of 11\(\beta\)-HSD-1.\(^6^7\) Insulin and IGFs suppress the synthesis of TNF-\(\alpha\) and IL-6, enhance the production of eNO, and show anti-inflammatory actions.\(^6^8-7^2\)

Insulin has anti-inflammatory actions.\(^6^8,7^0\) Insulin suppresses the production of TNF-\(\alpha\), IL-6, IL-1, IL-2, and macrophage migration inhibitory factor (MIF), which are pro-inflammatory molecules and enhances the production of IL-4 and IL-10 that are anti-inflammatory cytokines. This suggests that the presence and purpose of hyperinsulinemia in normal Indians is to prevent or abrogate the low-grade systemic inflammation that is inherent in them as evidenced by elevated levels of CRP, and possibly, TNF-\(\alpha\) and IL-6. On the other hand, leptin has pro-inflammatory actions.\(^1^1\) Since hyperinsulinemia and hyperleptinemia are evident in Indian children compared to white children,\(^7^3,7^4\) it is clear that features of low-grade systemic inflammation and metabolic syndrome X are initiated very early in life.

The distribution of body fat in Indians differs from that in the Western population. Indians have higher body fat or abdominal obesity even at normal range of BMI. This abdominal obesity or increased visceral fat seems to be a marker for the presence of insulin resistance and hyperinsulinemia that are considered as risk factors for the presence or development of hypertension, type 2 diabetes mellitus, hyperlipidemias, and CHD. It is not clear how and why Indians are more susceptible to develop abdominal obesity. Alternatively, is it also an indication of the presence of low-grade systemic inflammation?

Earlier I proposed that the activity of 11\(\beta\)-HSD-1 could be high in the adipose tissue of Indians secondary to enhanced plasma and tissue levels of CRP, IL-6, and TNF-\(\alpha\) compared to the Western white population.\(^7^5\) Such an elevated activity of 11\(\beta\)-HSD-1 explains the high incidence of abdominal obesity in Indians. Furthermore, as IGF-1 and insulin have a negative control on the activity of 11\(\beta\)-HSD-1, it is likely that insulin resistance and hyperinsulinemia seen in Indians since childhood in fact may be a protective phenomenon against the low-grade systemic inflammation. 11\(\beta\)-HSD-1 activities in adipose tissue are regulated by insulin, IGFs, TNF-\(\alpha\), and IL-6. The final expression of 11\(\beta\)-HSD-1 in adipose tissue, especially in the abdominal fat, depends on the balance between pro-inflammatory cytokines TNF-\(\alpha\) and IL-6 and insulin and IGFs that have anti-inflammatory action.\(^7^7\) When this balance tilts more towards TNF-\(\alpha\) and IL-6, the activity of 11\(\beta\)-HSD-1 is increased and this contributes to the development of abdominal obesity. In other words, the presence of abdominal obesity can be taken as an indication of the presence of elevated plasma/tissue levels of CRP, TNF-\(\alpha\), and IL-6; insulin resistance and hyperinsulinemia and decreased levels/activity of IGFs and insulin, and increased expression and activity of 11\(\beta\)-HSD-1 in abdominal adipose tissue. TNF-\(\alpha\) and IL-6 induce insulin resistance (they also reduce the levels of adiponectin) and decrease eNO synthesis. Elevated concentrations of TNF-\(\alpha\) and IL-6 are associated with low plasma HDL and elevated LDL levels, hypertriglyceridemia, hyperleptinemia, and glucose intolerance, abnormalities that are common in subjects with abdominal obesity. Thus, the presence of abdominal obesity can be considered as a physical sign of biochemical and immunological abnormalities: elevated levels of TNF-\(\alpha\), IL-6, lipids peroxides (since these cytokines stimulate free radical generation), LDL, oxidized LDL, hyperleptinemia, hypertriglyceridemia, and resistin; and low levels of HDL, eNO, adiponectin, IL-4, IL-10, and insulin resistance, hyperinsulinemia and glucose intolerance. These events ultimately lead to low-grade systemic inflammation and development of various other features of metabolic syndrome X in Indians.

If this is true, what is the initial event/stimulus that triggers the development of metabolic syndrome X? As insulin resistance is seen even in healthy Indian children,\(^7^7\) is it possible that the trigger for the development of metabolic syndrome X is present since childhood or even much earlier?

**Perinatal origin of metabolic syndrome X in Indians**

Both cardiovascular disease and type 2 diabetes may have its origins early in life.\(^9,1^1,6^9,7^6,7^7\) Low birth weight has been associated with high prevalence of metabolic syndrome X in later life.\(^6^9,7^8\) Indian babies are small, with low birth weights.
Metabolic syndrome X was 10 times greater in those who were 2.95 kg or less at birth compared with those whose birth weight were more than 4.31 kg. However, this has been disputed and suggested that much of what was claimed to be fetal in origin might, in fact, relate to postnatal nutrition and growth. This suggests that early nutrition has a bearing on the development of metabolic syndrome X in later life. If it is true that metabolic syndrome X has its origins in fetal life, improved obstetric care, general increase in the standard of living, and better nutrition during pregnancy are expected to decrease the incidence of metabolic syndrome X. Contrary to this, the incidence of obesity, type 2 diabetes, hypertension, and CHD have increased. It was reported that at all gestational ages at delivery, babies born to second-generation Asian women (women born in the United Kingdom) were heavier than those born to first generation Asian women (women born in the Indian subcontinent but residing in UK). The mean birth weight for babies of second-generation women was 3196 gm, 249 gm more than the mean birth weight of 2946 gm of babies of first generation women (P<0.001). It is possible that a similar trend towards an increase in the birth weight of babies born after 1970s is seen even in India. This implies that low birth weight could no longer account for the rapidly increasing incidence of metabolic syndrome X in Indians. If undernutrition is no longer responsible for the increasing incidence of metabolic syndrome X, is it possible that overnutrition has a role in its pathobiology in Indians?

**ω-3 and ω-6 Fatty Acids and Metabolic Syndrome X**

It is possible that factor(s) that influence fetal growth and development; modulate TNF-α, IL-6, IL-4, and IL-10 production; actions of insulin, and IGFs; and suppress 11β-HSD-1 activity might have a role in the metabolic syndrome X. Earlier I suggested that long-chain polyunsaturated fatty acids (LCPUFAs): eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), and arachidonic acid (AA) could be the endogenous molecules/factors that have an important role in the pathophysiology of metabolic syndrome X in Indians. It is possible that ω-3 and ω-6 fatty acids are essential for fetal growth and development including brain. Dietary linoleic acid (LA) and α-linolenic acid (ALA), which are essential fatty acids (EFAs), are desaturated and elongated to form their respective long-chain metabolites (Fig. 1 for metabolism of EFAs). Newborn infants, especially pre-term infants, have limited capacity to form EPA, DHA and AA. In infants, AA status correlated with one or more measures of normalized growth through 12 months. Dietary AA improves first year growth of pre-term infants possibly by stimulating glucose uptake by cells. EPA and DHA increase birth weight by prolonging gestation and/or by increasing the fetal growth rate. Some of the actions of LCPUFAs that are relevant to the present discussion include:

1. Ability of EPA and DHA to inhibit TNF-α and IL-6 production that accounts for their anti-inflammatory actions (reviewed in 69).
2. EPA, DHA and AA enhance eNO generation. This may, in part, explain why and how EPA and DHA are of benefit to protect against CHD. Further, the plasma phospholipid concentrations of EPA, DHA and AA were found to be low in subjects with hypertension, diabetes mellitus and CHD.
3. EPA, DHA and AA inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity and thus, regulate cholesterol metabolism (reviewed in 69). There is evidence to suggest that LCPUFAs may function as endogenous statins.
4. LCPUFAs function as endogenous ligands for PPAR-α and PPAR-γ and thus they possess some of the actions of thiazolidinediones. PPARs have anti-inflammatory actions (they suppress TNF-α and IL-6 production and inhibit free radical generation), and enhance the production of adiponectin. By functioning as ligands of PPARs, LCPUFAs enhance the production of adiponectin and prevent the progression of atherosclerosis.
5. EPA, DHA, and AA prevent insulin resistance. Both insulin resistance and hypertension was ameliorated in experimental animals by feeding them with EPA- and DHA-rich oil. Highly purified EPA reduced insulin resistance and decreased the incidence of type 2 diabetes in animal models of spontaneously type 2 diabetes. Decreased insulin sensitivity was found to be associated with decreased concentrations of EPA, DHA and AA in skeletal muscle phospholipids in humans.
6. EPA and DHA suppress leptin gene expression.
7. Metabolic syndrome X is uncommon in Greenland Eskimos whose tradition diet is rich in EPA and DHA.69
8. Normal Indians have significantly lower concentrations of AA, EPA, and DHA compared to healthy Canadians and Americans.100
9. When significant amounts of LCPUFAs are incorporated into the cell membrane, increase the number of insulin receptors on the cell membrane and their affinity to insulin by increasing membrane fluidity. On the other hand, saturated fatty acids decrease the number of insulin receptors on the cell membrane by decreasing membrane fluidity and thus, cause insulin resistance.69,101

Based on these data, it is suggested that metabolic syndrome X occurs in Indians due to perinatal deficiency of EPA, DHA and AA. For instance, maternal protein restriction or increased consumption of saturated and/or trans-fatty acids (which is increasing with the rapid westernization of dietary habits even in the Indian subcontinent) and energy rich diet during pregnancy decreases the activity of enzymes \( \Delta^5 \) and \( \Delta^6 \) desaturases that are essential for the conversion of dietary EFAs LA and ALA to their respective LCPUFAs. This leads to both maternal and fetal deficiency of EPA, DHA and AA. Perinatal protein depletion leads to almost complete absence of measurable activities of \( \Delta^6 \) and \( \Delta^5 \) desaturases in fetal liver and placenta.102 Thus, both protein deficiency and high-energy diet decrease the activities of \( \Delta^6 \) and \( \Delta^5 \) desaturases.

EPA, DHA, and AA have a negative feedback control on TNF-\( \alpha \) and IL-6 synthesis. Hence, EPA, DHA, and AA deficiency increases the generation of TNF-\( \alpha \) and IL-6 that in turn induce insulin resistance. Thus, maternal and fetal subclinical deficiency of EPA, DHA, and AA increase the levels of TNF-\( \alpha \) and IL-6 in the fetus. This is supported by the observation that that prenatal exposure to TNF-\( \alpha \) produces obesity,103 and obese children and adults have high levels of TNF-\( \alpha \) and IL-6.104,105 Furthermore, low plasma and tissue concentrations of EPA, DHA, and AA decrease production of adiponectin that in turn aggravates insulin resistance. Increased concentrations of TNF-\( \alpha \) and IL-6 enhance the activity of 11\( \beta \)-HSD-1 that leads to an increase in the production of corticosterone in the adipose tissue. This causes accumulation of adipose tissue in the abdomen, resulting in characteristic abdominal obesity seen in Indians and induces insulin resistance, and glucose intolerance.9,12,69.

CONCLUSIONS AND THERAPEUTIC IMPLICATIONS

It is evident from the preceding discussion that LCPUFAs, cytokines, maternal factors, 11\( \beta \)-HSD-1, adiponectin, and metabolic syndrome X. (+) Indicates increase in synthesis, action or disease process. (-) Indicates decrease in synthesis, action or disease process.

DHA, and AA in their plasma phospholipid fraction and various types of adipose tissues (such as mesenteric, subcutaneous, etc.,) compared to normal.

2. Serial measurement of plasma and tissue concentrations of EPA, DHA, and AA in the same individual at different ages can be correlated to the development of various features of metabolic syndrome X. It is predicted that children who are more prone to develop or those who are at high risk of developing metabolic syndrome X tend to show lower concentrations of these fatty acids. Thus, decreasing plasma or tissue concentrations of EPA, DHA, and AA compared to the baseline, may predict the development of metabolic syndrome X.

3. Increased plasma concentrations of CRP, TNF-\( \alpha \), IL-6, MIF, and adiponectin and/or decreased levels of IL-4 and IL-10 are expected in those who are at high risk to develop metabolic syndrome X and/or those who have abdominal obesity, hypertension, type 2 diabetes mellitus, hyperlipidemias or strong family history of any of these diseases compared to normal subjects.

4. Abdominal adipose tissue content of 11\( \beta \)-HSD-1, TNF-\( \alpha \), and IL-6 will be high both in obese subjects compared to European whites and normal Indians. Measurement of the concentrations of these biological markers in the adipose tissue may serve as markers of predicting the future development of metabolic syndrome X.

5. In those who are obese but who are not likely to develop other features of metabolic syndrome X may have normal levels of cytokines, 11\( \beta \)-HSD-1, and adiponectin both in
their plasma and adipose tissue. In such an event, serial measurements of these biomarkers (say once every year) may be necessary to know whether they continue to be normal or there are alterations in the concentrations of these markers.

If so what are the sequence of events that cause metabolic syndrome X? This could be as follows: intake of even normal amounts of carbohydrates, proteins, and fats and mixed meals cause an increase in the production of TNF-\(\alpha\) and IL-6 and consequently enhanced plasma CRP levels and a decrease in anti-inflammatory cytokines IL-4 and IL-10. TNF-\(\alpha\) and IL-6 cause oxidative stress and activation of NF-kB. These events cause insulin resistance and consequent hyperinsulinemia. In this instance, the function of insulin is not only to normalize plasma glucose, lipid and amino acid concentrations but also to serve as an anti-inflammatory molecule and suppress TNF-\(\alpha\) and IL-6 and enhance IL-4 and IL-10 synthesis. Both TNF-\(\alpha\) and IL-6 activate phospholipase A2 (PLA2) that in turn causes the release of LCPUFAs from the membrane lipid pool.\(^{106-108}\) These LCPUFAs when released in adequate amounts negatively control on the synthesis and release of TNF-\(\alpha\) and IL-6. As a result of this interaction, ultimately the balance between insulin and various cytokines; and pro- and anti-inflammatory cytokines is restored to normal. But, when chronic consumption of energy rich diet and/or saturated and trans-fatty acids and/or sub-optimal intake of LCPUFAs occurs, this leads to a state of low-grade systemic inflammation and chronic oxidative stress. On the other hand, dietary restriction and weight loss suppress free radical generation and oxidative stress,\(^ {109}\) and possibly, generation and release of TNF-\(\alpha\) and IL-6. Saturated and trans-fats interfere with the synthesis of LCPUFAs, and hence, normal inhibitory control exerted by LCPUFAs on TNF-\(\alpha\) and IL-6 will be defective or sub-optimal. This is supported by the observation that the intake of EPA and DHA but not ALA was inversely associated with plasma levels of sTNF-R1 and sTNF-R2 (soluble tumor necrosis factor receptors 1 and 2) and CRP whereas \(\omega-6\) fatty acids did not inhibit the anti-inflammatory effects of \(\omega-3\) fatty acids.\(^ {110}\) What is more interesting is the fact that a combination of both \(\omega-3\) and \(\omega-6\) fatty acids is associated with the lowest levels of inflammation. Thus, sub-clinical deficiency of or sub-optimal intake of EPA/DHA/AA/GLA/DGLA is expected to perpetuate low-grade systemic inflammation that ultimately leads to metabolic syndrome X (Fig. 3). Since these sequences of events happen throughout life, it is essential that LCPUFAs be provided right from pregnancy to prevent metabolic syndrome X.

If these proposals are true, what are its clinical implications? It is expected that adequate supplementation of EPA, DHA, and AA will help to prevent or postpone the development of metabolic syndrome X. It is possible that there could be individual variations in their response to EPA, DHA, and AA. Hence, it is suggested that suppression or normalization of plasma CRP, TNF-\(\alpha\), IL-6, and increase or normalization of plasma IL-4, IL-10, adiponectin, and adipose tissue 11\(\beta\)-HSD-1 can be used as markers to determine the adequacy of EPA, DHA, and AA administered. One of the major issues that need to be addressed is whether maternal supplementation of EPA, DHA, and AA prevents or postpones the development of metabolic syndrome X in their children. As a corollary to this, it is suggested that supplementation of adequate amounts of EPA, DHA, and AA since childhood (from birth to 15 years of age or even longer) decreases the incidence of metabolic syndrome X compared to those who were not given these fatty acids. This implies that those who have been adequately breast fed (human breast milk is rich in EPA, DHA and AA) or received adequate supplementation of EPA, DHA, and AA are likely to have decreased levels of 11\(\beta\)-HSD-1, TNF-\(\alpha\), and IL-6 in their adipose tissue and plasma.

Even those who already have metabolic syndrome X are likely to be benefited from the supplementation of EPA, DHA, and AA, although this is expected to be less dramatic. In such subjects perhaps a combination of exercise, weight reduction, anti-platelet agents, \(\beta\)-blockers, ACE (angiotensin converting enzyme)-inhibitors, insulin sensitizers, PPAR-\(\gamma\) and PPAR-\(\gamma\)-binding agents and EPA, DHA, and AA is...
necessary to provide therapeutic benefits beyond mere glucose lowering or control of hypertension.

There are several evidences that support some of the proposals made here. For instance, breast fed children have low incidence of obesity, hypertension, type 2 diabetes mellitus, insulin resistance and CHD in adulthood (reviewed in 9-12, 69); studies in experimental animals showed that DHA deficiency in the perinatal period can raise blood pressure later in life, even when animals were subsequently replete with this fatty acid. DHA-deficient animals underdrank water and overingested sodium, suggesting an aberration in central osmo/sodium sensors or angiotensinergic mechanisms. 111,112 This suggests that there is a critical window period during which adequate amounts of EPA, DHA, and AA should be made available to the fetus and newborn to prevent diseases in later life.112,113 This explains why EPA, DHA, and AA supplementation after the onset of metabolic syndrome X is not highly beneficial, and suggests that supplementation of LCPUFAs to pregnant women, infants, children, and adolescents is necessary to prevent metabolic syndrome X in later life.

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Announcement


Course Director : Milind Y Nadkar

Conference Dates and Venue

Workshop : Friday, 20th February, 2004 at SP Jain Auditorium Bombay Hospital and Research Centre, Mumbai


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