MINIREVIEW

Is Metabolic Syndrome X an Inflammatory Condition?

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It is suggested that metabolic syndrome X is a low-grade systemic inflammatory condition. Exp Biol Med 227:989–997, 2002

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The features of metabolic syndrome X include abdominal obesity, insulin resistance/hyperinsulinemia, dyslipidemia, type 2 diabetes mellitus, and hypertension (HTN), and this syndrome is associated with an increased risk of coronary heart disease (CHD) (1). Other factors associated with this metabolic syndrome or its consequences are hyperfibrinogenemia, increased plasminogen activator inhibitor-1 (PAI-1), low tissue plasminogen activator, nephropathy, microalbuminuria, and hyperuricemia (1). Insulin resistance and consequent hyperinsulinemia is present among these and develops early in the course of the syndrome (2). However, insulin resistance may not be the same and may not occur at the same time in all tissues of the body. For instance, adipose tissue is not resistant to insulin in the early stages of whole-body insulin resistance; the muscle, however, is resistant very early in the progression of the syndrome (3).

Prevalence of Metabolic Syndrome X

In the United States, by the year 2010, there may be about 50 to 75 million or more people with metabolic syndrome X. Though the exact reason is not known, it is more common on the Indian subcontinent. It may, in part, be due to genetic factors. The estimation of the prevalence also depends on the definition used to diagnose the syndrome. In general, all those who have type 2 diabetes, HTN, and CHD can be considered having this syndrome. It is likely that most persons with impaired glucose tolerance have metabolic syndrome X. Genetic makeup contributes to the development of metabolic syndrome X. However, why and how insulin resistance occurs is not clear. Recent studies suggest that low-grade systemic inflammation may play a role in the pathobiology of metabolic syndrome X.

What Causes Metabolic Syndrome X?

The presence of insulin resistance, which reflects a target cell or peripheral defect, is common in metabolic syndrome X. Hyperinsulinemia may be a consequence of this. By the time the diagnosis of diabetes is made, insulin resistance is already present. In type 2 diabetes, the insulin output is impaired in response to a given plasma glucose level or stimulus. However, it is not clear whether type 2 diabetes can occur without insulin resistance and an absolute impairment in insulin secretion. During the early phase of type 2 diabetes, there is usually a relative deficiency of insulin to compensate for increased serum glucose concentration. In fact, β cell is secreting an excess of insulin, suggesting that there is an early functional defect. It is likely that the glucose sensing mechanism of β cell is defective. Other factors that influence the development of metabolic syndrome X include adipose tissue and hormones secreted by it, abnormality of the hypothalamic-pituitary-adrenal (HPA) axis, advancing age, genetic (including CD36) (4) and environmental factors, and perinatal malnutrition (Fig. 1). A better understanding of factors that either precipitate or predispose an individual to develop metabolic syndrome X may pave way to develop newer methods of treatment or prevention. There is now evidence to believe that low-grade systemic inflammation, one factor that can interfere with

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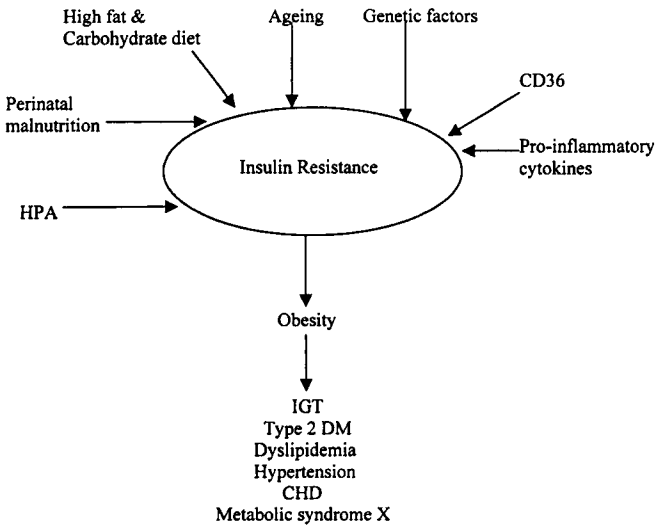

Figure 1. Scheme showing factors that can influence the onset of metabolic syndrome X. HPA, hypothalamo-pituitary-adrenal axis or system.

insulin action, seems to play a role in the pathobiology of various components of metabolic syndrome X such as obesity, insulin resistance, CHD, type 2 diabetes, and HTN.

Low-Grade Systemic Inflammation in Metabolic Syndrome X: Obesity

Though the etiology of obesity represents a complex interaction of genetics, diet, metabolism, and physical activity, there is considerable evidence to suggest that it could be an inflammatory condition. C-reactive protein (CRP) is a sensitive marker for systemic inflammation and is produced by the liver (5). A positive association between body mass index (BMI) and CRP has been described in otherwise healthy adults (6–8). Overweight children have increased concentrations of CRP compared with normal-weight children (9). A strong relation exists between elevated CRP levels and cardiovascular risk factors, fibrinogen, and high-density lipoprotein (HDL) cholesterol, suggesting that inflammation occurs throughout life in the development of atherosclerosis and cardiovascular disease.

Elevated CRP concentrations can be related to the increased expression and release of interleukin-6 (IL-6) by adipose tissue (10–12). IL-6, a pro-inflammatory cytokine, stimulates the production of CRP in the liver. In obese subjects, a strong correlation exists between obesity and IL-6 levels (13). IL-6 is essential for the induced expression of CRP (14), suggesting that elevated CRP levels are secondary to increase in IL-6 secretion.

Overweight and obese subjects showed increased serum levels of tumor necrosis factor-α (TNF-α), serum-soluble TNF receptor p55 (sTNF-RI), and serum-soluble TNF receptor p75 (sTNF-RII) compared with lean subjects (15, 16). Weight reduction or moderate-intensity regular exercise decreased the serum concentrations of TNF-α.

TNF-α, TNF-RI, and TNF-RII were negatively correlated with HDL cholesterol. Regular exercise decreased BMI, percentage body fat, glycolsylated hemoglobin (HbA_{1c}), serum TNF-α, sTNF-RI, and TNF-RII, and increased HDL cholesterol levels. Men in the highest quintile of plasma leptin weighed more, were less physically active, and had higher circulating insulin, C peptide, sTNF-RI, and sTNF-RII concentrations than men in the lowest quintile (17). This suggests that glucose homeostasis and the activity of TNF system modulate leptin secretion among overweight and obese men. Leptin upregulates phagocytosis and the production of IL-6 and TNF-α (18), whereas leptin-deficient mice (*ob/ob*) and rats that possess a defective leptin receptor (*fa/fa*) did not show the expected elevation in the levels of TNF-α and IL-6 in response to LPS. Leptin directly induces the release of IL-1 in the brain and mimics the action of IL-1 in the central nervous system (19). The effects of leptin on food intake and body temperature are mediated by IL-1. Thus, leptin influences the synthesis and release of pro-inflammatory cytokines. In this context, it is interesting to note that adipose tissue produces not only leptin, but also TNF-α and IL-6. Hence, one source for the increased levels of TNF-α and IL-6 observed in obese individuals could be adipose tissue itself.

Neurotansmitters, Pro-Inflammatory Cytokines, and Insulin Secretion

Neurotransmitters serotonin, dopamine, and neuropeptide Y (NPY) influence the synthesis and release of pro-inflammatory cytokines by their ability to alter acetylcholine (ACh) release in the brain. ACh suppresses the production of pro-inflammatory cytokines TNF, IL-1, IL-6, and IL-18, but not the anti-inflammatory cytokine IL-10 both *in vitro* and *in vivo* (20, 21). ACh is a potent stimulator of nitric oxide (NO) formation and release from endothelial cells (22). NO is a neurotransmitter and has a role in food intake. Serotonin, dopamine, and NPY modulate NO formation in the brain. TNF alters the metabolism of norepinephrine and the concentrations of serotonin and dopamine in the hypothalamus (23). Thus, there is a close interaction between various cytokines, neurotransmitters including leptin and ACh, NO, neuronal function, and food intake as discussed in detail elsewhere (20). This suggests that the low-grade systemic inflammation seen in obesity could be a reflection of increased concentrations of pro-inflammatory cytokines in the brain and in particular in the hypothalamus. These cytokines can cause neuronal cell death (24). Hence, the death of neurons that control the centers of appetite, satiety, and sense the adipose tissue content of the body may lead to loss of control on food intake and this eventually leads to obesity.

In this context, the relation between brain, plasma glucose levels, and the secretion of insulin from the pancreatic β cells is interesting. Long-term infusion of norepinephrine plus serotonin into the ventromedial hypothalamus (VMH) impairs pancreatic islet function in as much as VMH norpeinephrine and serotonin levels are elevated in hyperinsulinemic and insulin-resistant animals (25). Hence, it is pos-

sible that elevated concentrations of pro-inflammatory cytokines in the hypothalamus may damage the specific neurons that sense plasma glucose levels and control the secretion of insulin from pancreas. This may trigger the development of obesity. Because obese children tend to be obese adults, it is possible that obesity starts in infancy or even much earlier. This is evident from the observation that boys who were thin at birth tend to become obese if they were fed well and as a consequence have a higher incidence of CHD (26). This, coupled with the fact that breast-fed children have low incidence of obesity (27), suggests that events that occur during the fetal and early infancy have a bearing on the subsequent development of obesity. von Kries *et al.* (27) showed a clear dose-response effect for the duration of breast-feeding on the prevalence of obesity: the prevalence was 3.5% for 2 months of exclusive breast-feeding, 2.3% for 3–5 months, 1.7% for 6–12 months, and 0.8% for more than 12 months. Thus, perinatal events may program the infant's future propensity to develop obesity.

Low-Grade Systemic Inflammation and Insulin Resistance

In a population-based study, a statistically significant positive correlation between CRP and total cholesterol, triglycerides, BMI, glucose, and uric acid was observed, as well as a negative correlation between CRP and HDL cholesterol (28). In a multicenter, population-based study, a strong association between CRP and body fat (BMI and waist circumference), insulin sensitivity, and fasting insulin and proinsulin was reported (29). A linear increase in CRP levels with an increase in the number of metabolic disorders was noted. In a multivariate linear regression model, BMI, systolic blood pressure, and insulin sensitivity were related to CRP levels, suggesting that low-grade systemic inflammation occurs in insulin resistance syndrome.

Inflammation has a role in the pathogenesis of atherosclerosis (30), and atherosclerosis, in turn, is common in subjects with obesity, HTN, hyperlipidemia, diabetes mellitus, and insulin resistance. IL-6 levels are elevated in cardiovascular disease and are predictive of future ischemic events. It was reported that weekly injections of recombinant IL-6 resulted in significant increases in IL-6, IL-1β, and TNF-α, and fibrinogen levels, and increased atherosclerosis in C57B1/6 and ApoE-deficient mice compared with controls (31). This led to the conclusion that pro-inflammatory cytokines and acute phase proteins such as CRP participate in the development and progression of atherosclerosis.

CHD

One-half of all myocardial infarctions occur in persons in whom plasma lipid levels are normal (32). In a prospective study, higher levels of CRP were found among healthy postmenopausal women who subsequently had cardiovascular events than among those who did not have such events (33). CRP was found to be the strongest univariate predictor of the risk of cardiovascular events (34) in apparently healthy postmenopausal women over a mean follow-up period of 3 years. Patients with unstable coronary artery disease who had elevated levels of CRP were noted to be at higher risk of developing the long-term risk of death from cardiac causes (35). During a 5-year follow-up study, high plasma CRP concentrations were associated with a significant increase in CHD risk even after adjustment for lipid risk factors (36). In the Fragmin and Fast Revascularization During Instability in Coronary Artery Disease II trial, plasma circulating IL-6 levels showed a strong independent correlation to increased mortality in subjects with unstable coronary artery disease. Furthermore, early invasive treatment reduced 12-month mortality among those with elevated IL-6 levels, whereas mortality was not reduced among patients without elevated IL-6 concentrations (37). This supports the idea that low-grade systemic inflammation is involved in the pathogenesis of cardiovascular disease.

Leukocyte and blood myeloperoxidase levels were significantly greater in patients with established CHD than in controls (38). In a prospective study, the rates of myocardial infarction were lower in the aspirin group, and the magnitude of the beneficial effect of aspirin in preventing myocardial infarction was directly related to baseline levels of CRP measured at the beginning of the study when the participants were apparently healthy (39). The aspirin-assigned group showed a statistically significant reduction in the risk of myocardial infarction among men whose baseline CRP was in the highest quartile, suggesting that the benefit of aspirin is due to its anti-inflammatory effects (40).

It is known that multiple risk factors increase the probability of cardiovascular events (41). Risk factors tend to aggregate and usually appear in combination, and the clustering of risk factors is evident in childhood and persists into young adulthood (42–45). Multiple risk factors could accelerate atherosclerosis in these young people, which may start in childhood and the risk factors that may be present since then (46), including insulin resistance (47). Fatty streak formation, the precursor of atherosclerosis, and low-density lipoprotein (LDL) oxidation can be found in human fetal aortas and it is dependent on maternal hypercholesterolemia, suggesting that atherosclerosis starts during fetal life (48–50). This implies that interventions should be initiated in the fetal/perinatal period to prevent atherosclerosis and metabolic syndrome X.

Type 2 Diabetes Mellitus and HTN

In Pima Indians, fasting plasma IL-6 concentrations were positively related to adiposity and were negatively related to insulin action (51). Indian Asians in the U.K. have increased CHD mortality compared with European whites. CRP values were not only strongly associated with conventional CHD risk factors, but were also accounted for by greater central obesity and insulin resistance in Indian Asians (52). Elevated levels of CRP and IL-6 predicted the

development of type 2 diabetes mellitus, supporting a role for inflammation in the pathogenesis of diabetes mellitus (53). Subjects with elevated CRP levels at baseline testing were almost two times more likely to develop diabetes at 3–4 years of follow-up period (54). These results, coupled with the observation that TNF-α secretion was suppressed in the younger subjects but not in the older group in response to hyperglycemia (55), suggest that inflammatory process participates in the pathobiology of diabetes. Hyperglycemia induced the production of acute phase reactants from the adipose tissue (56). TNF-α plays a role in insulin resistance and type 2 diabetes mellitus (57). Thus, increase in the incidence of type 2 diabetes in the elderly age group could be linked to alterations in the homeostatic mechanisms that control TNF-α levels.

Both IL-6 and TNF-α produce insulin resistance (57, 58). Increased concentrations of circulating IL-6 and TNF-α observed could be a reflection of continuing neuronal damage in the hypothalamus. This may lead to alterations in the function of VMH, which in turn can impair pancreatic islet cell function. IL-6 has stimulatory action on the hypothalamic-pituitary-adrenal axis (59), which may lead to hypercortisolemia and consequent insulin resistance.

Low-grade systemic inflammation also plays a role in HTN. Increases in systolic and diastolic blood pressures, pulse pressure, and mean arterial pressure were significantly associated with levels of IL-6, whereas systolic blood pressure, pulse pressure, and mean arterial pressure were associated with levels of sICAM-1 (60). Elevated plasma IL-6 levels were significantly associated with systolic and diastolic blood pressures in women, whereas, in men, IL-6 was associated with fasting insulin and fasting insulin resistance index (58). Elevated plasma CRP levels also predicted the risk of future ischemic stroke and transient ischemic attack in the elderly (61).

An increase in the plasma levels of IL-6, TNF-α, and CRP observed in obesity, type 2 diabetes mellitus, hypertension, CHD, and insulin resistance, which are important components of metabolic syndrome X, suggests that low-grade systemic inflammation plays a significant role in these conditions. However, it is still debated whether inflammation is a primary event or a secondary event that causes these diseases. CRP levels do not seem to correlate with the extent of atherosclerosis. This suggests that CRP levels reflect the body's response to inflammation elsewhere in the body. On the other hand, studies showed that CRP functions as a chemoattractant, increases the expression of adhesion molecules, and activates complement proteins, which are important mediators of inflammation. Furthermore, CRP binds to LDL cholesterol and increases the uptake of LDL by macrophages. Studies in animals revealed that CRP enhances the size of infarction (reviewed in Ref. 62). These evidences lend evidence to the suggestion that inflammation plays a role in the pathobiology of metabolic syndrome X and diseases that are associated with it.

Perinatal Nutrition and Metabolic Syndrome X

Lower birth weight, an indicator of intrauterine nutrition, and higher BMI in childhood were associated with high prevalence of the metabolic syndrome X in later life (63). It was reported that of 64-year-old men whose birth weights were 2.95 kg (6.5 pounds) or less, 22% had metabolic syndrome X. The risk of developing metabolic syndrome X was almost 10 times greater in these men compared with those whose birth weights were more than 4.31 kg (9.5 pounds). It was suggested, however, that much of what was claimed to be fetal in origin may, in fact, relate to postnatal nutrition and growth (64, 65). This suggests that early nutrition has a bearing on the development of metabolic syndrome X in later life. It is likely that both fetal and postnatal nutrition influence susceptibility of an individual to develop metabolic syndrome X.

Prevention of Metabolic Syndrome X in Children and Adults

Based on the results of a prospective population-based cohort study, it was reported that obesity is of fundamental importance in the origin of metabolic syndrome X. This is supported by the observation that long-term calorie restraint sufficient to maintain a normal body weight and prevention of middle-age onset obesity in nonhuman primates prevented insulin resistance (66).

Both weight reduction and exercise decreased the incidence of diabetes in middle-aged, overweight subjects with impaired glucose tolerance (IGT) compared with the control group (67). The data from the Nurses' Health study showed that overweight or obesity was the single most important predictor of type 2 diabetes (68). Subjects who exercised for a mean of 2.5 hr/week, showed an increased ability of mononuclear cells to produce anti-inflammatory cytokines IL-4 and IL-10, and transforming growth factor-β (TGF-β) rose by 36% and serum CRP declined by 35% (69). Exercise significantly enhanced the activity of manganese superoxide dismutase (MnSOD), which paralleled the reduction in the magnitude of myocardial infarction (70). Administration of the neutralizing antibodies to TNF-α and IL-1β abolished the cardioprotective action of exercise and also the activation of MnSOD. This suggests that production of free radicals and TNF-α and IL-1 induced by exercise leads to activation of MnSOD, which plays a major role in the cardioprotective action induced by exercise (71). TNF-α levels were lower in pregnant women who exercised (72). Further, weight loss achieved by a low-calorie diet produced significant decreases in serum and adipose tissue IL-6 levels (73). This suggests that exercise has anti-inflammatory and antioxidant actions and thus, abrogates insulin resistance.

Atherosclerosis, Exercise, Pro-Inflammatory Cytokines, and NO

Atherosclerosis is common with advancing age. Aging impaires endothelial NO (eNO) synthesis and enhances en-

dothelial cell apoptosis. In aged human vein umbilical endothelial cells (HUVECs), oxidized LDL (ox-LDL) and TNF-α-induced apoptosis and caspase-3-like activity were significantly enhanced compared with young cells (74). NO protects endothelial cells via S-nitrosylation (S-NO) of caspases. Aged HUVECs show significantly reduced eNOS expression and a decrease in the overall S-NO of proteins. Endothelial cells with eNOS knockout showed enhanced apoptosis induction, whereas exogenous NO donors abolished increased apoptosis and caspase-3-like activity. Upregulation of NO synthesis in response to shear stress is the mechanism by which apoptosis was inhibited in young cells. On the contrary, no upregulation of eNOS protein expression and S-NO content in response to shear stress was detected in aged cells. Overexpression of wild-type eNOS completely restored the antiapoptotic effect of shear stress. TNF-α induces apoptosis of endothelial cells by inhibiting eNO synthesis and via S-NO of caspases (74, 75). Exercise enhanced eNO synthesis and reduced TNF-α production, lowered plasma cholesterol, and decreased atherosclerotic lesions by 40%, and concomitantly increased arterial catalase and endothelial NO synthase activity (76). Thus, exercise prevents atherosclerosis by stimulating arterial antioxidant response, and eNO synthase, and by suppressing pro-inflammatory cytokine synthesis and release (see Fig. 2). However, it may be noted here that, paradoxically, the initial stimulus for the upregulation of antioxidant enzymes in exercise comes from the enhanced production of TNF-α induced during the phase of exercise itself. TNF-α, IL-6, IL-1, and interferon-γ (IFN-γ) enhance inducible NO (iNO) synthesis. Targeted disruption of iNO protectes against obesity-linked insulin resistance (77). Exercise decreases the production of TNF-α and IL-6, and thus, reduces the production of iNO, which may account for the ability of exercise to reduce insulin resistance. These actions of exercise explain why it is effective in the prevention and treatment of obesity, diabetes mellitus, HTN, hyperlipidemia, atherosclerosis, CHD, and insulin resistance.

It is interesting to note that breast-fed infants have a lower incidence of obesity, insulin resistance, HTN, diabetes mellitus, and CHD (27, 78, 79). This suggests that some constituent(s) of the breast milk may render them to resist the development of these diseases. Breast milk is rich in long-chain polyunsaturated fatty acids (LCPUFAs). I suggest that LCPUFAs could be a major factor that influences the development of metabolic syndrome X in adult life.

LCPUFAs, Low-Grade Systemic Inflammation, and Metabolic Syndrome X

Insulin resistance and metabolic syndrome X are common in Indian Asian adults and children compared with European whites (47). CRP concentrations were higher in healthy Indian Asians than in European whites, which accounted for greater abdominal obesity and insulin resistance seen in Indian Asians (80, 81). Both insulin resistance and

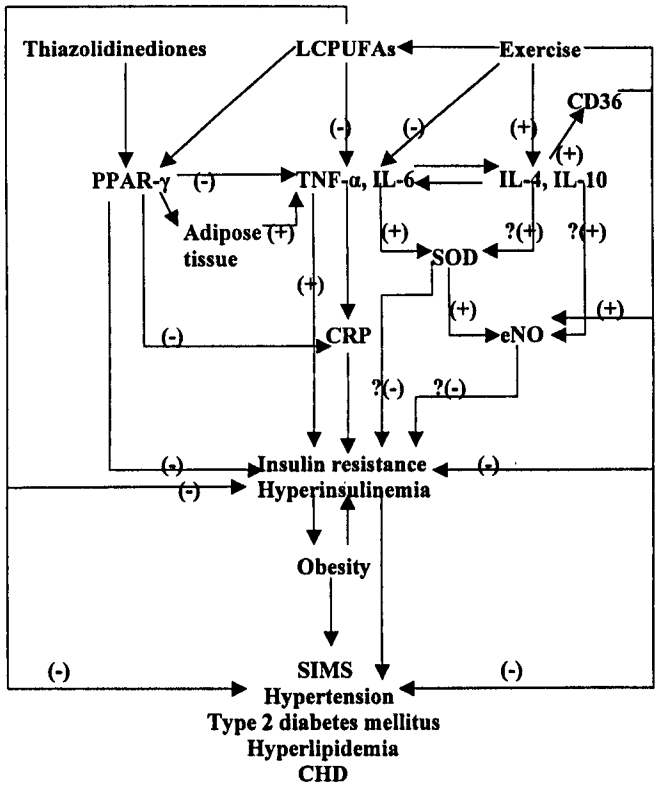

Figure 2. Scheme showing the relationship between exercise, cytokines, CRP, LCPUFAs, SOD, and eNO and insulin resistance or SIMS. SOD is known to increase the half-life of eNO. + indicates enhancement of action, synthesis, or formation and induction of insulin resistance and/or SIMS. – indicates decrease in synthesis, action, or formation, and prevention of insulin resistance. ? indicates that this relationship needs to be established but is expected to be (+) or (–).

metabolic syndrome X are much less common in Greenland Eskimos on a traditional diet, which is rich in ω-fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Normal Indian Asians have significantly lower concentrations of arachidonic acid (AA), EPA, and DHA than normal, healthy adult Canadians and Americans (Minnesotans) in their plasma phospholipids (82). Compared with Eskimos, Canadians and Americans have lower levels of these fatty acids. LCPUFAs, especially EPA and DHA, have a negative feedback control on the production of TNF-α and other pro-inflammatory cytokines (reviewed in Ref. 20). The low plasma LCPUFA content seen in Indian Asians may lead to an increase in the production of pro-inflammatory cytokines, which in turn may predispose them to develop insulin resistance and other features of metabolic syndrome X (see Fig. 2).

LCPUFAs may attenuate insulin resistance. For instance, fructose-induced insulin resistance and HTN can be ameliorated by feeding the rats with EPA- and DHA-rich oil (83). Highly purified EPA ethyl ester can reduce insulin resistance and decrease the incidence of type 2 diabetes in OLETF and WBN/Kob rats, respectively (models of spontaneous type 2 diabetes mellitus), by modifying the phospholipid fatty acid composition of the skeletal muscle mem-

brane (84, 85). Decreased insulin sensitivity was found to be associated with decreased concentrations of LCPUFAs in skeletal muscle phospholipids in humans (86, 87). An inverse relationship between fasting plasma insulin and the percentage of AA in erythrocyte fatty acids was noted in healthy humans (88). Based on this, it is suggested that subclinical or marginal deficiency of LCPUFAs from the perinatal period may lead to an increase in the production of pro-inflammatory cytokines TNF-α, IL-6, IL-1, and IL-2, which in turn predisposes to the development of insulin resistance and other features of metabolic syndrome X (Fig. 2). This is supported by the observation that patients with type 2 diabetes, HTN, and CHD have low plasma concentrations of LCPUFAs (82). Thus, metabolic syndrome X is an inflammatory condition and its high incidence in certain populations such as Indian Asians is due to their low intake of ω-3 fatty acids and/or low activity of δ-6- and δ-5-desaturase enzymes, which are critical for the formation of LCPUFAs.

Conclusions

It is evident from the preceding discussion that almost all components of metabolic syndrome X are associated with low-grade systemic inflammation. In view of the presence of systemic inflammatory response in metabolic syndrome X, "systemic inflammatory metabolic syndrome" (SIMS) may be a more appropriate term to describe it. It is suggested that SIMS could be due to a marginal or subclinical deficiency of LCPUFAs from early infancy. If this is true, can this proposal explain the close association seen between low birth weight and the higher risks of type 2 diabetes, HTN, CHD, and metabolic syndrome X (89) seen in later life, anandamides and obesity, and the role of adiponectin, CD36, and 11β hydroxysteroid dehydrogenase type 1 (11β HSD-1) activity and visceral fat accumulation seen in humans?

Growth retardation due to maternal protein restriction decreased δ-6-desaturase activity in the low-protein offspring (90). Mercuri *et al.* (91) reported that prenatal protein depletion led to almost complete absence of measurable activities of δ-6- and δ-5-desaturases in fetal liver and placenta, which are necessary for the formation of LCPUFAs from their precursors. As already discussed, low levels of LCPUFAs increase TNF-α synthesis. Furthermore, prenatal exposure to TNF-α produces obesity (92), and obese children and adults have high levels of TNF-α (see above).

LCPUFAs have also been shown to regulate leptin gene expression (93). Oral supplementation of LCPUFAs increases the concentrations of anandamides in the brain (94), which in turn bind to endogenous cannabinoid receptors and regulate food intake (95). Thus, provision of adequate amounts of LCPUFAs during the perinatal period would ensure the generation, presence, and function of the appropriate number of cannabinoid receptors in the brain. This in turn is expected to ensure that food intake is maintained at optimum level and prevents the onset of obesity in adult life.

Adiponectin, an adipose tissue derived protein, has antiangiogenic properties and suppresses adhesion molecule expression in vascular endothelial cells and cytokine production from macrophages. Thus, adiponectin behaves as an anti-inflammatory molecule. Concentrations of adiponectin were found to be low in patients with insulin resistance. Peroxisome proliferator-activated receptor-γ (PPAR-γ) ligands significantly increased the plasma adiponectin levels in insulin-resistant humans (96). Because LCPUFAs serve as endogenous ligands for both PPAR-α and PPAR-γ, by virtue of this property, they may enhance the concentrations of adiponectin and this could be one mechanism by which they (LCPUFAs) reduce insulin resistance. On the other hand, CD36, a class B scavenger receptor involved in angiogenesis, atheroslcerosis, inflammation, and lipid metabolism, overexpression in skeletal muscle decreases fat deposition and enhances transport of LCPUFAs (97). It is possible that decreased expression of CD36 in South Asians could be one genetic factor that induces insulin resistance and abdominal obesity in these populations because downregulation of CD36 seems to be associated with inflammation. PPAR-γ ligands, thiazolidinediones, and IL-4 increase CD36 expression. Thus, CD36 connects inflammation, LCPUFAs, PPAR-γ, IL-4, obesity, and atherosclerosis. Transgenic mice overexpressing 11β HSD-1 selectively in adipose tissue developed visceral obesity and exhibited insulin-resistant diabetes, hyperlipidemia, and hyperphagia despite hyperleptinemia (98). Thiazolidinediones, which are ligands for PPAR-γ, markedly reduce adipocyte 11β HSD-1 mRNA both *in vitro* and *in vivo* and thus are able to preferentially reduce visceral fat accumulation in humans. LCPUFAs, which also bind to PPARs, may have a similar inhibitory action on 11β HSD-1 activity. However, this remains to be tested. Based on this, it is suggested that expression of CD36 and 11βHSD-1 can be used a markers of low-grade inflammation (in addition to plasma CRP, TNF-α, and IL-6 concentrations) and to predict future development of obesity, HTN, and atherosclerosis.

The beneficial effect of aspirin in reducing all-cause mortality may, at least partly, be mediated through its anti-inflammatory rather than its antiplatelet properties (99). Physical activity lowers the concentrations of CRP, fibrinogen, white blood cells, factor VIII, IL-6, and TNF-α, and enhances the levels of anti-inflammatory cytokines IL-4 and IL-10, suggesting that exercise reduces systemic inflammation (20). Thus, treatment aimed at improving insulin resistance such as exercise and weight reduction using metformin, insulin sensitizers, and PPAR-γ-binding agents and ω-3 fatty acids may provide therapeutic benefits beyond mere glucose lowering. It remains to be seen whether perinatal supplementation of LCPUFAs can indeed help in the prevention of obesity, HTN, type 2 diabetes, and other features of metabolic syndrome X or SIMS.

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