Metabolic Syndrome: A Disease of the Brain

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Abstract: *Background:* There is evidence on the relation between brain dysfunction and pathogenesis of metabolic syndrome leading to cardiovascular diseases, type 2 diabetes and insulin resistance.

Methods: Medline search till Dec, 2009 and articles published in various national and international journals were reviewed. Experts working in the field were also consulted.

Results: Increased intake of refined carbohydrates, linoleic acid, saturated and total fat and low dietary n-3 fatty acids and other long chain polyunsarurated fatty acids (PUFA) in conjunction with sedentary behaviour and mental stress and various personality traits can predispose inflammation and central obesity. There may be increased sympathetic activity with increased secretion of catecholamine, cortisol and serotonin and proinflammatory cytokines that appear to be underlying mechanisms of metabolic syndrome. Excess secretion of these neurotransmitters in conjunction of underlying long chain PUFA deficiency, may damage the neurons *via* proinflammatory cytokines, in the ventromedial hypothalamus and insulin receptors in the brain, especially during fetal life, infancy and childhood, resulting into their dysfunction. Since 30-50% of the fatty acids in the brain are long chain PUFA, especially omega-3 fatty acids, which are incorporated in the cell membrane phospholipids, it is possible that their supplementation may be protective. Omega-3 fatty acids are also known to enhance parasympathetic activity and increase the secretion of anti-inflammatory cytokines IL-4 and IL-10, as well as acetylecholine in the hippocampus. It is possible that marginal deficiency of long chain PUFA, especially n-3 fatty acids, due to poor dietary intake during the critical period of brain growth and development in the fetus and infant, and also possibly in the child, adolescents and adults, may enhance the release of tumor necrosis factor-alpha, interleukin-1, 2 and 6 and cause neuronal dysfunction. Experimental studies indicate that ventromedial hypothalamic lesion in rats induces hyperphagia, resulting into glucose intolerance and insulin resistance. Treatment with neuropeptide Y abolished the hyperphagia and ob mRNA (leptin mRNA) in these rats. Long term infusion of norepinephrine and serotonin into the ventromedial hypothalamus, impaired pancreatic islet function in as much as, ventromedial hypothalamic norepinephrine and serotonin levels are elevated in hyperinsulinemic and insulin resistant animals. Treatment with insulin was associated with restoration of these hypothalamic neurotransmitter abnormalities indicating that a dysfunction of ventromedial hypothalamus can impair pancreatic beta cells resulting into metabolic abnormalities consistent with metabolic syndrome. Treatment with omega-3 fatty acids, coenzyme Q10, meditation, active prayer, beta blockers, ACE inhibitors, and oestrogen may have a beneficial influence on insulin receptors and ventromedial hypothalamic dysfunction. However, no definite and precise insight into the patho-physiological link between metabolic syndrome and brain and nutrition is available. Despite this weakness, epidemiological studies and intervention trials indicate that treatment with n-3 fatty acids may be applied to clinical practice and used to direct therapy for prevention of metabolic syndrome, type 2 diabetes, hypertension, coronary artery disease, and atherosclerosis.

Keywords: Glucose intolerance, Insulin resistance, brain disease, diet, nutrition, n-3 fatty acids, brain development, brain-heart connection.

INTRODUCTION

Recent studies indicate that there is coexistence of nutritional deficiencies and appreciable overnutrition in the form of central obesity and overweight in developing countries, which in part may be due to brain-body interactions [1-15]. The Global Burden of Disease Study clearly showed that the gratifying gains in cardiovascular health occurred in developed countries, in association with an epidemic of cardiovascular (CVD) in the developing world. The world has been in a position to learn, the mechanism of transition from poverty to economic development and emergence of CVD. We proposed that overweight comes first in conjunction with hyperinsulinemia, increased angiotensin activity and central obesity followed by glucose intolerance, type 2 diabetes, hypertension, low HDL and hypertriglyceridemia (Metabolic syndrome). This sequence is followed by (CAD), gall stones

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and cancers and finally dental caries, gastrointestinal diseases and bone and joint diseases, during transition from poverty to affluence. As people become rich, they begin to increase their dietary fat, salt and sugar intake in the form of ready prepared foods, syrups, dairy products and flesh foods in place of grain based diet. There is a greater use of automobiles, television viewing and decrease in sports, walking and dancing as recreation. These changes in the diet and lifestyle in conjunction with increased tobacco and alcohol intake, appear to be basic factors in the pathogenesis of metabolic syndrome [1-3]. The first decade of the last century offered us an opportunity to initiate action to counter growing epidemics of CVD including metabolic syndrome on both sides of the atlantic. When people learned the methods of prevention, there was a decrease in CVD in the western world but obesity continued to increase, resulting into an increase in the metabolic syndrome in both developed and developing economies [1-5].

Metabolic Syndrome

Clustering of risk factors may accur with obesity, in particular central obesity, which may be associated with impaired glucose tolerance, with an adverse lipid profile and hypertension and may be seen as early as in childhood and adolescence. These risk factors which are indicator of metabolic syndrome also tend to be clustered in children and adolescents with unhealthy lifestyles and diets such as those with excessive intakes of saturated fats, cholesterol and salt and inadequate consumption of dietary fibre. Decrease in physical activity and increased television viewing are other factors which further increase the risk [1-3]. In older children and adolescents, habitual alcohol and tobacco use also contribute to high blood pressure and to the development of other risk factors in early adulthood which continue to act in later life course. Such clustering of risk factors which is characteristic of metabolic syndrome represents an opportunity to address more than one risk factor at a time and may be due to clustering of health related behaviours.

Of the several characteristics of metabolic syndrome, at least 3 should be present for its diagnosis. Obesity in conjunction with type 2 diabetes, hypertension, coronary artery disease (CAD), and dyslipidemia are important features of the metabolic syndrome which is usually associated with hyperinsulinemia and insulin resistance. Several names have been given by various investigators for this entity;insulin resistance syndrome, Reaven's syndrome, deadly quartet, CHAOS, new world syndrome, civilization syndrome, syndrome X and finally metabolic syndrome which is also now accepted by the World Health Organization. We know that metabolic syndrome occurs due to interaction of environmental factors and genetic susceptibility [16]. However, genetic do not mean nonnutritional or that genetic predisposition can not be modulated. There is consistent evidence that dietary factors and physical activity, mental stress and environmental toxicants influence gene expression and have shaped the genome over several million years of human evolution. There is opportunity for health, as well as susceptibility to diseases, through genes, while environmental factors determine which susceptible individuals will develop metabolic syndrome. Rapid changes in diet and lifestyle due to socioeconomic changes provide added stress causing exposure of underlying genetic predisposition to chronic diseases such as type 2 diabetes, obesity, hypertension, CAD and atherosclerosis. Several studies are continuing on the role of nutrients in gene expression [16]. It is not clear how n-3 fatty acids suppress or decrease the mRNA of interleukin, which is elevated in atherosclerosis, arthritis and other autoimmune diseases, whereas n-6 fatty acids have no such effects [16]. Metabolic syndrome appears to be polygenic in nature and rapidly escalating rates suggest the importance of environmental change, rather than changes in genetic susceptibility [3-6].

COMPONENTS OF METABOLIC SYNDROME

In the 1960s-1970s, Albrink described the cluster of obesity with high plasma triglycerides and hyperinsulinemia as being a risk factor for the development of CAD. In 1988, Reaven, in the Banting lecture, suggested the role of clustering of insulin resistance, glucose intolerance, hypertension, hyperinsulinemia, increased VLDL triglycerides, and decreased plasma high density lipoprotein (HDL) cholesterol as risk factors for development of type 2 diabetes and cardiovascular diseases [3-6]. Several additional components have been recognized in later years such as; increased small dense low density lipoprotein (LDL) cholesterol, fibrinogen, plasminogen activator inhibitor-1, microalbuminuria, endothelial dysfunction, hyperuricemia, -angiotensin activity and proinflammatory cytokines and other factors. Experimental studies indicate that several of the components of metabolic syndrome may have their origin in the brain, a hypothesis proposed by Das in connection with type 2 diabetes [17].

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Environmental factors causing damage during fetal life may have lifetime consequences, which may be described as programming or adaptations or microcompetitions [1-6, 18]. The damage to the neural and psychiatric mechanisms may continue during infancy, childhood and in the later years of life [18]. The hormonal signals, nutritional factors and environmental toxicants may serve as signals for programming or adaptations. It is possible that these protective mechanisms developed during scarcity, serve to program the development of insulin resistance, central obesity, hypertension, type 2 diabetes, and CAD in later life, due to dysfunction of the brain. As described earlier, metabolic syndrome is characterized by insulin resistance and hyperinsulinemia, CAD, type 2 diabetes, obesity, dyslipidemia and atherosclerosis. Increased concentrations of proinflammatory factors; tumor necrosis factor-alpha (TNF-alpha), C-reactive protein and deficiency of anti-inflammatory cytokines, interleukin 4 and 10, have been documented in obesity, insulin resistance, glucose intolerance, type 2 diabetes, hypertriglyceridemia, CAD and atherosclerosis that are important components of metabolic syndrome [19, 20]. Apart from TNF-alpha, interleukin-1, 2 and 6 are also proinflammatory and may be raised in metabolic syndrome. The exact mechanisms, how proinflammatory factors cause their adverse effects, are not clear. However, TNF-alpha could be decreased by long-chain PUFA, especially, n-3 fatty acids and may be enhanced due to their deficiency [21, 22]. It seems that TNF-alpha may participate in the pathogenesis of metabolic syndrome by two mechanisms; primarily by inducing insulin resistance and secondarily by interfering with functions of ventromedial hypothalamus.

The human brain is quite rich in long chain polyunsaturated fatty acids (PUFA) such as arachidonic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [23-25]. These fatty acids are neuroprotective and constitute 30% to 50% of the total fatty acids in the brain, where they are predominantly associated with membrane phospholipids [25]. Therefore, if there is a deficiency of long chain PUFA, especially during the critical period of brain growth known to damage the neurons [21-25]. TNF-alpha may also damage suprachiasmatic nucleus, pineal and pituitary glands, olfactory bulb and the hypothalamus, the last three are rich in insulin receptors which are important in the metabolic syndrome.

Ventromedial Hypothalamus AND Metabolic Syndrome

Experimental studies [26-28] indicate that ventromedial hypothalamic lesion in rats can cause hyperphagia and excessive weight gain in association with glucose intolerance, hyperglycemia, hyperinsulinemia and hypertriglyceridemia that are classical manifestations of metabolic syndrome. Local infusion of antibodies against neuropeptide Y inhibited the hyperphagia and ob mRNA (leptin mRNA) in these animals. Another experiment [29], showed, selectively lower levels of norepinephrine and dopamine in the hypothalamus of rats with ventromedial hypothalamic lesion. Infusion of norepinephrine plus serotonin into the ventromedial hypothalamus impaired pancreatic islet function in as much as ventromedial hypothalamus norepinephrine and serotonin levels are elevated in hyperinsulinemic and insulin resistant animals [30]. Treatment with insulin restored the levels of neurotransmitters in the hypothalamus. It is possible that ventromedial hypothalamus dysfunction can impair pancreatic beta-cell function and induce metabolic abnormalities characteristc of metabolic syndrome.

There is evidence that increased release or better action of neuropeptide Y may be responsible for hyperphagia and obesity in ventromedial hypothalamic lesioned animals and that the ob gene is upregulated even in nongenetic obesity [28, 31]. In a further experiment, [32] streptozotocin-induced diabetic rats showed greater rise in neuropeptide Y levels in the paraventricular, ventromedial and lateral hypothalamic areas indicating that most areas of the hypothalamus can influence the pathogenesis of metabolic syndrome. The hyperphagic and obese ventromedial hypothalamic lesioned rats may have suppressed splenic natural killer cell activity, which predisposes proinflammatory responses [33]. These responses may become worst if there is underlying deficiency of long chain PUFA in the hypothalamus and other vulnerable parts of the brain. The brain cells generate interferon-alpha, interleukin (IL)-1, IL-2 and TNF-alpha.

In response to various stresses [34, 35] one experiment in rats showed that TNF-alpha lowered the firing rate of the ventromedial hypothalamus neurons indicating that a close association exists between hypothalamic monoamines, islet cell function and cytokines which may regulate insulin resistance and development of metabolic syndrome [36].

Metabolic Syndrome and Insulin Receptors in the Brain

Experiment in female NIRKO mice [37] revealed greater food consumption and food sensitive obesity with increases in body fat and plasma leptin levels, insulin resistance, hyperinsulinemia and hypertriglyceridemia, which are classical manifestations of metabolic syndrome. It seems, that reduction in the number of insulin receptors, poor function of insulin receptors and insulin deficiency or resistance in the brain, result into development of metabolic syndrome, despite normal pancreatic beta cells. This experiment also showed that intraventricular injection of insulin inhibited the food intakes in the animals [37]. However, neuron specific disruption of the insulin receptor gene (NIRKO) in the mice may not interfere with brain development and neuronal survival.

There is evidence that insulin signaling can regulate food intake, neuronal growth and differentiation by influencing neurotransmitter release and synaptic plasticity in the brain [37, 38]. As mentioned earlier, the brain is rich in insulin receptors, particularly in the hypothamus, pituitary and olfactory bulb [39, 40]. There is an increase in neuropeptide Y levels in paraventricular nucleus on food deprivation, which returns to control range after insulin administration, without altering blood glucose levels. Similar changes were observed on peripheral insulin administration. Sahu *et al.* [41] showed that insulin and insulin –like growth factor-II (IGF-II) reduced the release of neuropeptide Y in a dose dependent fashion from the paraventricular nucleus *in vitro*. It is possible that the site of insulin action on the hypothalamic neuropeptide network is at the level of Neuropeptide Y nerve terminals and that insulin and IGF-II reduce, neuropeptide Y secretion from the paraventricular nucleus [41]. Since neuropeptide Y is a potent orexigenic signal and because insulin and IGF-II reduce hypothalamic neuropeptide Y levels, it is possible that optimal amount of insulin, insulin receptors and IGF-II in the brain might decrease appetite and food intake resulting into modulation of metabolic syndrome. One experiment [42], in rats fed ad libitum, administered glucose or insulin caused increased extracellular acetylecholine in the amy-Gdala. Acetylecholine is known to reduce dopamine secretion [43] and low levels of dopamine, may enhance appetite [44]. Acetylecholine also prevents the synthesis and release of TNF-alpha *in vitro* and *in vivo* [45]. Therefore, it is possible that one major function of insulin, IGF-II and acetylecholine in the brain is to protect neurons from the death signals of TNF-alpha, IL-1, 2 and 6.

Polyunsaturated Fatty Acids and Insulin Receptors

Salem *et al.* [46], have described that adequate amount of arachidonic acid, DHA are necessary for optimal development and physiological function of the central nervous system. Essential fatty acids; linoleic acid and alpha linolenic acid convert into arachidonic acid and DHA in the infants by elongation and desaturation. PUFAs accumulate in the brain during the last trimester of fetal life and the first few months of infancy. These fatty acids appear to have beneficial effects on cell membrane and neural tissue. Decreased supply of these fatty acids in the infant formula milk based on vegetable oil may result into suboptimal neural development and dysfunction due to decreased brain PUFAs content [46, 47]. The main sources of arachidonic acid, EPA and DHA for accumulation in infants may be, maternal to placental transfer, consumption of breast milk, and synthesis from linoleic acid and alpha-linolenic acid. Arachidonic acid regulates the energy metabolism in the cerebral cortex by stimulating glu-

cose uptake by the cortical astrocytes [48]. Increased availability of glucose increases acetylecholine release in the brain [49]. It is clear that arachidonic acid enhances acetylecholine release by enhancing glucose.

Uptake in the brain. Similarly, DHA is known to enhance cerebral acetylecholine levels and improve learning ability in rats [50]. Obesity is an important component of metabolic syndrome, which may be associated with fewer dopamine receptors and lower dopamine levels [44]. Acetylecholine interacts with dopamine receptors in the hippocampus [51] and modulates neuronal functions such as long-term potentiation and synaptic plasticity in neuronal circuits.

There is an increased formation of PUFAs from their precursors as a result of desaturation, augmented by insulin and calorie restriction. The synapses in the central nervous system contain the insulin receptor and the insulin receptor tyrosine kinase substrate p58/53 [4].

Thus long chain PUFAs and insulin, both potentiate each other in providing neuroprotection against damage due to proinflammatory cytokines. Arachidonic acid, HHA and other PUFAs are Neuroprotective and are potent inhibitors of IL-1, IL-2 and TNF-alpha generation [21]. Insulin and IGF-1 can prevent TNF-alpha induced neuronal damage [23, 24].

Excess of linoleic acid may enhance oxidative stress whereas insulin and longchain PUFAS regulate superoxide anion generation which may increase the production of endothelial nitric oxide (eNO) [52-55]. NO can quench free radicals and is anti-inflammatory [56]. There is some evidence that IGF-1 and possibly insulin may increase acetylecholine release from the Cortical slices [57] which has anti-inflammatory activity and is a potent stimulator of eNO synthesis [58]. It is possible to conclude that insulin, IGF-1, acetylecholine, longchain PUFAs

Inhibit the production of TNF-alpha and augment the synthesis of eNO aAcetylecholine and eNO are neuroprotective as well as interact with other neurotransmitters. It is possible that PUFAs most important function is to ensure adequate number of insulin receptors in the brain. If adequate amount of PUFAs are not incorporated in the neuronal cell membranes during the fetal development and infancy, it may cause a defect in the expression or function of insulin receptors resulting in to type 2 diabetes. PUFAs present in the cell membranes maintain their fluidity which enhances the number of insulin receptors and the affinity of insulin to receptors resulting into improvement in insulin sensitivity [59-63].

CLINICAL EVIDENCE ON METABOLIC SYNDROME AND POLYUNSATURATED FATTY ACIDS

Epidemiological studies indicate a strong association between the method of infant feeding in the first weeks after birth and glucose tolerance in adults aged 48-53 years [64, 65]. It is possible that presence of long chain PUFAs in the breast milk may be the cause of the negative associat- ion between breast feeding and insulin resistance and type 2 diabetes (metabolic syndrome). The decline in breast feeding may also be the cause of recent increase in the prevalence of type 2 diabetes, hypertension and CAD in certain populations like south Asians (8-10). In south Asians, fetal undernutrition and greater prevalence of metabolic syndrome compared to Caucasians And Chinese have also been described [66-68]. In Pima Indians [69, 70], bottle-fed children had significantly greater prevalence of type 2 diabetes compared to breast-fed children. In one study [64], bottle fed subjects showed a higher mean 2-hour plasma glucose level after oral glucose tolerance test compared to breast-fed subjects. In another study [65], breast fed children showed a significantly higher percentage of DHA and total percentage of long chain PUFAS in muscle phospholipids and lower plasma glucose levels compared with bottle fed subjects. An inverse correlation between fasting glucose and the percentage of DHA and total long chain PUFAs was also observed [59]. Since, human breast milk is rich in long chain PUFAs; gama-linolenic acid, dihomo-gama-linolenic acid, arachidonic acid, EPA and DHA, therefore the beneficial effects of breast feeding in prevention of metabolic syndrome may be attributed to these fatty acids.

One study [71] showed a significant association between insulin secretion and action and arachidonic acid. In another study [72], an inverse association was found between fasting plasma insulin and the percentage of arachidonic acid in erythrocyte fatty acids. A lower insulin sensitivity was associated with lower levels of PUFAs in skeletal muscle phospholipids in healthy subjects [59]. These findings clearly indicate that PUFAs can modulate insulin sensitivity and insulin resistance and also possibly metabolic syndrome. No beneficial effects were found in blood glucose and insulin mediated glucose uptake, when treatment with fish oil for 6 months was administered to patients with established type 2 diabetes [73]. It seems that major actions of PUFAs are directed to prevention of insulin resistance, hypertension, and type 2 diabetes and may be least effective when these diseases are set in. This finding also explains the association between breast feeding and decline in the incidences of insulin resistance, diabetes and hypertension [63, 65, 69, 74, 75]. However, in patients with CAD, the role of n-3 fatty acids has been found to be useful in many studies [76-78], although, effects on brain function were not reported in these studies.

In infants, especially those who are preterm, the synthesis of long chain PUFAs from alpha-linolenic acid and linoleic acid is inadequate in the early stages of life [79-81]. A marginal deficiency of PUFAs during the critical phases of fetal and infant growth may have a major adverse effect on subsequent health. The development, expression and maintainance of insulin receptors therefore, due to inadequate PUFAs is low and the concentrations of proinflammatory cytokines TNF-alpha, responsible for neurodegeneration would be greater [82]. An underlying deficiency of PUFAs and higher levels of cytokines, may be associated with decreased expression and number of insulin receptors in the brain and damage to ventromedial hypothalamus resulting into development of metabolic syndrome. Weisinger *et al.* [83], also showed that a deficiency of DHA in the perinatal period can cause hypertension in later life, despite when deficiency was repaired with this fatty acid in animals subsequently. Since hypertension is a manifestation of metabolic syndrome, DHA deficiency causing metabolic syndrome is good possibility.

Food consumption is quite essential in the development of obesity, which is an important determinant of metabolic

syndrome. Since PUFAs can regulate food intake, it is possible that long chain PUFAs consumption may influence the development of obesity and and type 2 diabetes which are components of metabolic syndrome. Long chain PUFAs can modulate the endogenous lipids N-acetyl-ethanolamine (anandamide) and 2-acyl-glycerols, the ligands of cannabinoid receptors that are important for food intake and satiety. Breast milk is a rich source of long chain PUFAs as well as several other bioactive chemical substances. It is possible that PUFAs interact with other nutrients, hormones and bioactive factors present in the breast milk to fine tune their beneficial actions by their ability to influence cell membrane fluidity, expression of receptors on the membranes and subsequent postreceptor events [75]. Since breast milk and long chain PUFAs can independently modulate obesity, insulin resistance, hypertension, diabetes mellitus and coronary artery disease (metabolic syndrome) in later life, it is possible that the beneficial actions of breast milk may be attributed to its rich content of long chain PUFAs [59, 65, 70, 74, 75, 84, 85].

Polyunsaturated Fatty Acid Administration and Accumulation

It is not clear where and how much, long chain PUFAs should be available to prevent the development of metabolic syndrome. Apart from brain, long chain PUFAs are also required by the endothelium, kidney, heart, liver and other tissues for their normal functions. It is possible that long chain PUFAs administyration (through breast milk or mothers nutrition) during the critical periods of growth (third trimester to second year, postterm) accumulate in the special areas of the brain as well as in vessel walls including endothelium, heart and kidneys, pancreas, and liver;the organs involved in metabolic syndrome. Therefore these organs are able to modulate the pathobiochemical, and neurobiological mechanisms that tend to induce metabolic syndrome In one study [86], erythrocyte phospholipid arachidonic acid and DHA levels of the umbilical cord vein were significantly lower in women with gestational diabetes compared to healthy pregnant subjects. This study also showed that glycosylated hemoglobin in mothers was inversely associated to fetal erythrocyte DHA and arachidonic acid in gestational diabetes mellitus. It may be due to fetal impairment in accretion of these fatty acids indicating that a decline in the accumulation of perinatal long chain PUFAs enhances the risk of diabetes. In another study [87], A high fat, low carbohydrate diet decreased the ability of insulin to modulate endogenous glucose production. A further study [88] showed that substituting dietary saturated fat for monounsatu rated fat impaired insulin sensitivity in health subjects. In a longterm follow up study [89, 90].

Long chain PUFAs (especially n-3) caused significant decline in the risk of diabetes after 14 years. These studies indicate that supplementation of PUFAs in healthy subjects can protect them against diabetes which is a component of metabolic syndrome. Fetal growth retardation inhibits delta-5-desaturase activity which is a key enzyme in the formation of long chain PUFAs. Supplementation of long chain PUFAs through infant feed formula may repair this block resulting into decline in the incidence of metabolic syndrome [91-93]. One experimental study [94] further supports this view which showed a decrease in the ratio of DHA to EPA as a result of low delta-5-desaturase activity in hepatic microsomes of retarded offsprings, in conjunction with higher fasting plasma insulin levels. It seems that the origin of arachidonic acid in the breast milk is neither due to the conversion of linoleic acid nor it is derived from direct intestinal absorption. In lactating women, maternal body stores could be the major sources of linoleic acid and arachidonic acid in the breast milk. It is important therefore to provide long chain PUFAs to women from external sources to maintain their body stores [95]. This strategy would be useful for the fetus during pregnancy for development of insulin receptors and hypothalamus. There is a need to provide adequate amount of PUFAs to infants from birth to 2 year postterm which is critical period of brain and somatic growth [96]. Since brain can produce neurons at any age, it may be useful to supply PUFAs in later life for prevention of metabolic syndrome [97]. To determine whether supplementation of infant formula milk with long chain PUFAs influences blood pressure in later childhood, 147 formula fed children with a reference group of 88 breast fed children were studied for 6 years [98]. Results revealed that 67 children in the PUFAs group (64% of original) and 76 in the non-supplementation group (60%) Were enrolled into the follow up study. The PUFAs group had a significantly lower mean blood pressure, systolic (-3. 0mmHg, 95% confidence interval -5. 4 to 0. 5 mmHg) and diastolic (-3. 6 mm Hg, 95% confidence interval –6. 5 to –0. 65 mmHg) than the non-supplementation group. The diastolic blood pressure of the breast fed children was significantly lower than that of the non-supplemented formula group but did not differ from the PUFA formula group.

An interaction between the nervous and immune systems has been suggested for more than 70 years which explains how diet or acupuncture or psychological states or yogic exercises Might influence inflammatory or immunological diseases [99, 100]. Hong Wang and colleagues show that activation of nicotinic acetylecholine receptors on macrophages reduces the release of proinflammatory cytokines;TNF-alpha and IL-1 and IL-6, induced by endotoxin lipopolysaccharide [99]. There is direct evidence that vagal nerve stimulation, acting through these receptors, can reduce inflammatory responses. Since long chain PUFAs can stimulate vagal nerve induced acetylecholine levels, it is possible that these fatty acid might influence nicotinic acetylecholine receptors and may be beneficial in lung disease.

Metabolic Syndrome and Circadian Rhythm

The rhythm of every day life is controlled by the molecular biological clock, situated in the brain's suprachiasmatic nucleus. It is under the strong influence of daily light and darkness, and under weak influence of plasma melatonin levels secreted by the pineal gland [14, 15, 101-103]. It is possible that long chain PUFAs, especially DHA and EPA content, of the neurons situated around suprachiasmatic nucleus and pineal gland may be important in the pathogenesis of circadian rhythm of cardiac events and insulin resistance. Low content of long chain PUFAs can enhance the sensitivity of suprachiasmatic nucleus to light, leading to a greater surge of cateclolamines, resulting into excess formation of TNF-alpha, IL-1, IL- 2 and IL-6 that are proinflammatory cytokines. These cytokines are known to damage various target organs responsible for metabolic syndrome.

A circadian cycle is present in every cell which is controlled by neurotransmitters, autonomic system including our neuroendocrine time structures [102, 103]. Triggering of suprachiasmatic nucleus due to deficiency of long chain PUFAs and other environmental factors may activate sensors, receptors and hormones (pineal gland, pituitary functions and adrenal secretions) resulting into increase in adverse effects on circadian variations, heart rate variability (HRV) and blood pressure variability (BPV) [101-105]. There is evidence that saturated and total fat intake may enhance sympathetic activity with an increase in catecholamines, cortisol, serotonin and oxidative stress, whereas treatment with omega-3 fatty acids can inhibit sympathetic activity by enhancing parasympathetic activity leading to increased secretion of acetylecholine in the hippocampus [101] which may blunt the release of proinflammatory cytokines and enhance the release of anti-inflammatory cytokines.

Several studies [106-109] have reported the existence of a peak in the morning hours, in a study of acute myocardial infarction (AMI). The subsequent reports from other countries and the extensive data by WHO in the report of myocardial infarction Community Registers [107-109] from 19 European centers, clearly demonstrated a peak incidence of the onset of chest pain due to AMI from 8:01 to 11:00 a. m. with a ratio of approximately 2:1. In one study from India [105], in 605 patients of AMI, those who had Q wave infarction (n=174) showed that 39% had the onset between 6. 00 a. m. to 12. 00 noon. In a more recent study among 202 patients of AMI, the incidence of onset of chest pain was highest in the second quarter of the day (41. 0%), mainly between 4:00 a. m. to 8:00 a. m. which was followed by fourth quarter, usually after large meals (28. 2%). Emotion, the second trigger (43. 5%) was more common in patients with the onset of chest pain in the second quarter of the day (51. 8%). Cold weather was a predisposing factor in 29. 2% and hot temperature (>40 degree C) was common in 24. 7% of the patients. Blood pressure was also lower in the night and morning while it increased in the daytime.

HRV refers to the regulation of sinoatrial node, which is the natural pacemaker of the heart by the sympathetic and parasympathetic branches of the autonomic nervous system. It is possible that beat-to-beat fluctuations in the cardiac rhythm provide us with an indirect measure of heart health as defined by the degree of balance in sympathetic and vagus nerve activity. BPV and HRV may be quantified by around-the-clock serial measurement of blood pressure and heart rate as well as holter electrocardiographic monitoring in the ward or clinic; these may be analysed by computer-implemented curve-fitting to assess the about 24 hour (circadian) variation among other rhythmic and chaotic components of the time structure (chronome) [2]. Since PUFAs can influence, cytokine levels in the cardiac, vascular and neuronal tissues, including, hippocampus acetylecholine levels, causing increased parasympathetic activity, it is possible that HRV and BPV, may be under influence of dietary long chain PUFAs.

Recent studies indicate that low HRV is a predictor of arrhythmic cardiac death, myocardial infarction, rapid progression of atherosclerosis and death from heart failure [110-113]. Low HRV may also be a risk factor of metabolic syndrome by enhancing proinflammatory cytokines and hyperinsulinemia. Similarly metabolic syndrome may have adverse effects on HRV and BPV. There are circadian rhythms for plasma levels of catecholamines, cortisol, renin, angiotensin, aldosterone, insulin and serotonin [111-117]. These hormones are also important in the damage to ventromedial hypothalamus and insulin receptors, which are known to regulate insulin resistance and therefore metabolic syndrome. The brain-heart interactions through HRV as well as BPV appear to be under the influence of lifestyle and nutritional factors including long chain PUFAs [118-125]. Christensen and co-workers [118] studied the dietary supplementation with n-3 fatty acids on HRV, in a randomized controlled trial in 81 patients with postmyocardial infarction. There as a significant increase in HRV compared with controls in the intervention group, indicating that PUFAs supplementation causing, an increased vagal cardiac tone may be beneficial in these patients. In a further study [119], these investigators reported that without dietary supplementation with n-3 fatty acids, there was a positive correlation between HRV and the content of n-3 fatty acids (docosahaexaenoic acid, DHA) in platelets in postmyocardial infarction patients with left ventricular dysfunction. This study also showed a negative correlation between the ratio of arachidonic acid /DHA and SDNN which is in line with earlier results, showing that this ratio is high in the heart muscle of men who die of SCD compared with controls [120]. The increment in HRV seemed to be due to the intake of 1 fish meal per week with an increase in SDNN from 103 ms to 122ms. Singh and co-workers in one randomized, controlled intervention trial [121], among 118 (fish oil group) and 122 (control group) patients with acute myocardial infarction, showed that treatment with fish oil was associated with significant reduction in cardiac events in the intervention group compared to control group (30 vs. 56, P<0. 02) after a follow-up of 1 year. While the majority of cardiac events were reported in the second (35. 7 vs. 16. 0%, P<0. 0l) and fourth (28. 5 vs. 16%, P<0. 05) quarters of the day, compared to first (16. 0%) and third (19. 6%) quarter of the day, in control group, no such association was observed in fish oil group. The findings suggest that fish oil administration may have modulated circadian rhythm of cardiac events. The exact mechanism by which n-3 fatty acids increase HRV is not known but *in vitro* studies suggest that these fatty acids have beneficial effects on cardiac myocytes and neurones, similar to calcium blockers [123]. There is strong evidence that n-3 fatty acids may inhibit sympathetic nervous activity and increase vagal tone which enhances the secretion of acetylecholine, resulting into increased HRV [124]. However, all n-3 fatty acids do not provide the protection against adverse effects of autonomic dysfunction [124]. In a recent intervention trial [125], treatment with alpha-linolenic acid which is a short chain n-3 fatty acids, showed no benefit in patients with low HRV. In a more recent study by Christensen *et al.* [126], each of the 291 patients that were referred for coronary angiography had completed a food questionnaire regarding fish and wine intake. The n-3 fatty acid composition of granulocyte membranes and of adipose tissue was measured and 24 hour HRV was analysed. Fish intake was positively associated with the level of n-3 fatty acids in adipose tissue. Significant positive correlation were found between HRV indices and the levels of n-3 fatty acids in granulocytes. Wine intake was also positively correlated with HRV, but this correlation was no

longer significant after controlling for the cellular level of n-3 fatty acids. The positive association between n-3 fatty acids and HRV in patients with CAD indicates that n-3 fatty acids have a protective effect against HRV and possibly sudden cardiac death. It has been demonstrated that n-3 fatty acids incorporate in the phospholipids of the cell membrane and stabilize the excitatory neurones, cardiomyocyte and arterial smooth muscle as well as endothelial cells [124].

Risk Factors AND Protective Factors

Age, sedentary habits, coronary artery disease, hypertension, diabetes, obesity, insulin resistance, pollution, hyperlipidemia, and hyperglycemia are risk factors of decreased HRV, and most of these factors are under influence of diet and lifestyle [127-139]. These factors are also components or risk factors of metabolic syndrome.

The effects of physical activity, exercise training, and breathing patterns on HRV have been studied in a number of studies [127-131]. Epidemiological studies indicate that increased physical activity may be associated with lower concentrations of proinflammatory cytokines TNF-alpha and IL-1 and IL-6 which may have a beneficial effects on the insulin receptors and hypothalamus. Physical inactivity is an important risk factor of metabolic syndrome and regular exercise is a most powerful tool in its management. The heart beats about 100, 000 times each day in human adults and changes in the cardiac frequency are of diagnostic importance among other features of circulation. Exercise training as part of a comprehensive cardiac rehabilitation program has been shown to improve morbidity and mortality rates in patients after myocardial infarction. It is possible that benefits of cardiac rehabilitation may be achieved through an altered cardiovascular autonomic tone, improvement in the functioning of insulin receptors and ventromedial hypothalamus. Exercise training has beneficial effect on autonomic tone as well as on various components of metabolic syndrome.

We know that increased plasma fatty acids can stimulate sympathetic nervous system in animals. A recent study [135], in healthy subjects (20 intervention and 10 controls) were randomly assigned to receive an infusion of lipid emulsion or saline in the two groups respectively. Lipid emulsion infusion was associated with a rise in plasma epinephrine and norepinephrine concentrations in the experimental group compared to controls. The increase in plasma fatty acids was associated with a significant decline in RR interval and in total power. Analysis of different components of HRV showed that lipid emulsion infusion stimulated low frequency components at the second hour and at the third hour. Therefore, the low frequency/high frequency ratio was significantly stimulated at the second and the third hour. Such results persisted, although attenuated, when the study was repeated in association with propranolol infusion. It is possible that hyperlipidemia may stimulate cardiac autonomic nervous system activity resulting into a decrease in HRV whereas betablockade may be protective [135].

Since previous studies demonstrated a reduced HRV among diabetics, holter electrocardiography was done in 1919 subjects, in a population based study at Framingham [136]. HRV variables included the SD of normal RR intervals (SDNN), high frequency (HF, 0. 15 to 0. 40 Hz) and low frequency (LF, 0. 04 to 0. 15 Hz) power, LF and HF power, and LF/HF ratio were inversely related to plasma glucose levels. SDNN and LF and HF powers were reduced in diabetes and in subjects with impaired fasting glucose levels [136]. Short-term increases in particle air pollution have been associated with increases in daily cardiovascular mortality and morbidity in studies from cities throughout the industrialized world [139]. We understand that in response to particle exposure, heart rate or rhythm abnormalities without hypoxia or respiratory distress may be present, indicating that particle air pollution may influence cardiovascular function. In one study [139], among 21 Boston residents, the association between ambient pollution levels and cardiovascular function through HRV were studied. The protocol involved 25 minutes per week of continuous Holter electrocardiographic monitoring. The findings showed that particle and ozone exposure may decrease vagal tone, resulting in reduced HRV [139].

Mechanisms for Brain-Heart Connection

It is possible that neurohumoral activation and altered sympathovagal interaction, due to changes in the fatty acid, as well as phospholipid content of cell membranes of neurones and cardiac cells are the most common mechanisms of abnormal HRV of patients with heart disease. These cells may also be under influence of fatty acids, aminoacids and glucose. These nutrients are the chemical substances that are necessary to life processes such as metabolism, reproduction, motility and sensation. The nutrients found in food cannot be detected unless they interact specifically with appropriate components such as ligand binding proteins that may be linked to processes for their uptake or utilization. Glucose provides both energy to pancreatic beta cells and generates a signal that promotes insulin secretion. The functions may also be separate as in the use of glutamic acid for neuronal protein synthesis or for neurotransmission. Total and saturated fatty acids enhance sympathetic activity and catecholamines secretion and n-3 fatty acids increase the vagal activity and acetylecholine secretion. The melatonin secretion increases with darkness at night, which is beneficial to neurohumoral system, resulting into increased vagal tone and greater secretion of acetylcholine. However, daylight is associated with increased plasma concentration of cortisol and higher sympathetic activity resulting into cardiovascular dysfunction. Therefore, eating a heavy breakfast in the morning in conjunction with stress of the day and daylight may have multifold adverse effects on the brain-heart dysfunction resulting into greater cardiac events in the second quarter of the day [12, 17]. Treatment with Indo-Mediterranean diet was protective against circadian rhythm of cardiac events indicating that w-3 rich diet can influence brain heart interactions [17].

MANAGEMENT

Meditation, exercise training, breathing exercises, trimetazidine, beta-blockers, ACE-inhibitors, n-3 fatty acids, oestrogens, ubiquinone, spironolactone have been observed to have beneficial effect on HRV and BHV [110, 118-126]. Mediterranean diet and Indo-Mediterranean diet due to rich content of w-3 fatty acids may also influence brain- beta cell connection and improve insulin sensitivity.

Experimental evidence suggests that aldosterone may have detrimental effects on the autonomic nervous system, especially during the morning hours. It is possible that spironolatone therapy given in addition to angiotensin converting enzyme inhibition may improve survival in CHF. In a recent study [140] by Yee *et al.* , 28 patients with NYHA class II and III heart failure received 50 mg spirolactone daily and placebo for 4 weeks each, in a double-blind crossover fashion. After each treatment phase, a full circadian assessment was undertaken of its autonomic effects. Spironolactone significantly reduced all indices of QT dispersion. The reductions in Qtcmax, QTd and QTcd were greatest at 6 a. m. In addition, spironolactone had favourable autonomic effects which were limited to morning including heart rate reduction and improvement in HRV. Betablockers in CHF act by improving autonomic dysfunction however, patients with profound neurohumoral abnormalities derive better survival benefit. In one study [141] by Aronson and Burger, time and frequency domain HRV indices were obtained from 24 hour Holter recordings and compared to assess the role of betablockade in 199 patients with decompensated heart failure. All HRV indices were markedly suppressed but were substantially higher in patients who were on betablockers. Time domain measures parasympathetic cardiac activity, the percentage of RR intervals with >50ms variation and the squire root of mean squired differences of successive R-R intervals were higher in betablocker group. Spectral analysis revealed that the total power and ultra low frequency power were significantly higher in patients on betablockers (82% vs 59%). The high frequency power, a spectral index of parasympathetic modulation, was 41 % higher in the betablocker group. Norepinephrine and interleukin-6 levels were substantially lower in patients on betablockers (28% and 61 % respectively), although these differences were not significant. It is clear that betablockers improve the impaired cardiac autonomic regulation during high sympathetic stress of decompensated CHF which plays an important role in the protection of myocardium and prevention of arrhythmias during transient increases in sympathetic activity. In a further study [142] by Lin *et al.* , reported benefical effects of betablockers on HRV.

In acute MI, the biochemical findings simulate the presence of metabolic syndrome due to presence of hyperglycemia, hypertriglyceridemia, hyperinsulinemia and low high density lipoprotein cholesterol. HRV is also depressed due to increased sympathetic activity and/or decreased parasympathetic tone resulting into electrophysiological changes such as increased ventricular late potentials in the cardiovascular system. In one study [143], in 64 patients, 31 received trimetazidine plus other drugs while the remaining 33 patients were studied as controls. After treatment, HRV parameters reflecting parasympathetic activity were significantly higher in the trimetazidine group, whereas the low frequency component indicating sympathetic activity was similar in both groups. In addition, low frequency/high frequency ratio showing sympatho-vagal balance was significantly decreased in the trimetazidine group. Antidiabetic drugs such as pioglitazones, gliclazide and metformin are known to improve insulin sensitivity and dyslipidemia, and can be useful in metabolic syndrome [145]. It seems that drug therapy, in conjunction with nutritional management including Mediterranean diet and Indo-Mediterranean diet; low linoleic acid and no trans fatty acids and refined carbohydrates, reduction of weight, whole grains, fruits, vegetables and nuts, may be protective [146-156]. In a double-blind, randomized and placebo-controlled study involving 30 young women, supplementation with zinc was associated with decrease in anger and depression [157]. The women were randomized to one of two groups for a period of 10 weeks: 1) zinc group: (n=15) received multivitamins + zinc (7 mg/day); control group: (n=15) received multivitamins daily. Women in the zinc group showed significant reduction in anger-hostility score and depression-dejection score (P=0. 011) in the Profile of Moods State (POMS). Zinc deficiency may also cause insulin resistance and may be associated with decreased insulin receptors in the brain.

In brief, it is clear that there is a beneficial role for betablockers, trimetazidine, spironolactone, n-3 fatty acids and meditation and active prayer in the management of HRV and therefore in the modulation of brain-heart connection. Apart from these agents, zinc, chromium, magnesium, ACE inhibitors, statins, fibrates, glitazones, metformin as well as dietary approaches should also be considered protective to brain, cardiovascular system and beta cells of pancreas in the prevention of metabolic syndrome *via* modulation of neural and cardiovascular mechanisms [144-158].

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