EDITORIAL

Nutritional Predictors and Modulators of Insulin Resistance

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Given the rapidity with which traditional diets and lifestyle are changing in Asia, it is interesting to find that food insecurity and undernutrition persist in the same community where chronic diseases are emerging as a major epidemic [1–10]. Malnutrition, characterized by intrauterine growth retardation and deficiency of iodine, vitamin A and energy, was the major cause of death and disability in developed and newly industrialized countries, and is still a problem in the developing world [1–3]. There is coexistence of nutritional deficiencies and appreciable overnutrition in the form of central obesity and overweight among Asians [6–13]. We propose that overweight comes first, in conjunction with hyperinsulinaemia, increased angiotensin activity and central obesity followed by glucose intolerance, type 2 diabetes, hypertension, low high-density lipoprotein (HDL) and hypertriglyceridaemia (metabolic syndrome). This sequence is followed by coronary artery disease (CAD), gallstones and cancers and finally dental caries, gastrointestinal diseases and bone and joint diseases, during the transition from poverty to affluence. Economic gains are associated with an increase in dietary fat, salt and sugar intake in the form of ready-prepared foods, syrups, dairy products and flesh foods in place of a phytochemical-based diet. There is a greater use of automobiles, television viewing and a decrease in sports, walking and dancing as recreation. These changes in nutritional and lifestyle factors, in conjunction with an increased tobacco and alcohol intake, appear to be basic factors in the pathogenesis of insulin resistance including metabolic syndrome [1–3]. A diet rich in n-3 fatty acids, monounsaturated fatty acids (MUFAs), zinc, chromium, selenium, and antioxidant vitamins has been suggested to be beneficial in insulin resistance, whereas an increase in total and saturated fat and refined carbohydrates may cause hyperglycaemia and hyperinsulinaemia predisposing to insulin resistance [2–11].

INSULIN RESISTANCE AND METABOLIC SYNDROME

A clustering of risk factors may occur with obesity, in particular central obesity, which may be associated with hyperinsulinaemia, impaired glucose tolerance, with an adverse lipid profile and hypertension and may be seen as early as in childhood and adolescence. These risk factors, indicators of insulin resistance which determines 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, n-3 fatty acids and phytochemicals. Sedentary behaviour, such as increased television viewing without spare time physical activity, is another factor which further increases 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 hyperinsulinaemia and insulin resistance in early adulthood which continue to act in later life. Such a clustering of risk factors characteristic of insulin resistance and metabolic syndrome represents an opportunity to address more than one risk factor at a time and may be due to the clustering of health-related behaviours. As insulin resistance almost always results in insulin resistance syndrome, if untreated, it is important to consider this problem.

Of the several characteristics of insulin resistance syndrome, at least three should be present for its diagnosis. Obesity in conjunction with type 2 diabetes, hypertension, CAD, and dyslipidaemia are important features of metabolic syndrome which is usually associated with hyperinsulinaemia and insulin resistance. Several names have been given by various investigators for this entity: Reaven’s syndrome, the deadly quartet, CHAOS, new world syndrome, civilization syndrome, syndrome X and finally metabolic syndrome, which is also now accepted by the World Health Organization. In this issue of the Journal of Nutritional & Environmental Medicine, a study by Hwalla et al. [13] demonstrated that an increased intake of a monounsaturated fat-rich diet can reverse insulin resistance, which is quite interesting.

Many workers propose that insulin resistance occurs due to an interaction of environmental factors and genetic susceptibility [14]. However, genetic does not mean non-nutritional or that the genetic predisposition cannot 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 the opportunity for health, as well as susceptibility to diseases, through genes, while environmental factors determine which susceptible individuals will develop insulin resistance. Rapid nutritional transition, due to socio-economic changes, provides added stress, causing the exposure of the underlying genetic predisposition to hyperinsulinaemia and insulin resistance, leading to type 2 diabetes, obesity, hypertension, CAD and atherosclerosis. Several studies are continuing on the role of nutrients in gene expression [14]. It is not clear how n-3 fatty acids suppress or decrease the messenger ribonucleic acid (mRNA) of interleukin (IL), which is elevated in atherosclerosis, arthritis and other autoimmune diseases, whereas n-6 fatty acids have no such effects [14]. Insulin resistance 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 INSULIN RESISTANCE AND METABOLIC SYNDROME

The capability of insulin to lower circulating glucose levels, stimulate glucose utilization (muscle plus fat) and suppress glucose production (liver) is insulin sensitivity. A condition of low insulin sensitivity is insulin resistance which results in metabolic syndrome. In the 1960s–1970s, Albrink described the cluster of obesity with high plasma triglycerides and hyperinsulinaemia as being a risk factor for the development of CAD. In 1988, Reaven, in the Banting Lecture, suggested the role of the clustering of insulin resistance, glucose intolerance, hypertension, hyperinsulinaemia, increased very low-density lipoprotein (VLDL) triglycerides, and decreased plasma HDL cholesterol as a risk factor for the 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, hyperuricaemia, angiotensin activity and proinflammatory cytokines and other factors. Animal experiments indicate that several of the components of metabolic syndrome may have their origin in the brain [15].

INSULIN RESISTANCE: A DISEASE OF THE BRAIN

Diet and lifestyle factors causing damage during fetal life may have lifetime consequences, which may be described as programming, adaptations or microcompetitions [1–6, 16]. The damage to the neural and psychiatric mechanisms may continue during infancy, childhood and in the later years of life [16]. 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 programme 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 hyperinsulinaemia, CAD, type 2 diabetes, obesity, dyslipidaemia and atherosclerosis. Increased concentrations of proinflammatory factors, tumour necrosis factor-alpha (TNF-alpha), C-reactive protein and deficiency of antiinflammatory cytokines, IL-4 and IL-10, have been documented in obesity, insulin resistance, glucose intolerance, type 2 diabetes, hypertriglyceridaemia, CAD and atherosclerosis that are important components of metabolic syndrome [17, 18]. Apart from TNF-alpha, IL-1, IL-2 and IL-6 are also proinflammatory and may be raised in metabolic syndrome. The exact mechanisms of how proinflammatory factors cause their adverse effects are not clear. However, TNF-alpha could be decreased by long-chain polyunsaturated fatty acids (PUFAs), especially n-3 fatty acids, and may be enhanced due to their deficiency [19, 20]. 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 the ventromedial hypothalamus.

The human brain is quite rich in long-chain PUFAs such as arachidonic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [21–23]. These fatty acids are neuroprotective and constitute 30–50% of the total fatty acids in the brain, where they are predominantly associated with membrane phospholipids [23]. Therefore, if there is a deficiency of long-chain PUFAs, especially during the critical period of brain growth from the third trimester to infant age (2 years), it may cause increased levels of TNF-alpha which is known to damage the neurones [19–23]. TNF-alpha may also damage the suprachiasmatic nucleus, pineal and pituitary glands, the olfactory bulb and the hypothalamus; the last three are rich in insulin receptors which are important in metabolic syndrome.

THE VENTROMEDIAL HYPOTHALAMUS AND INSULIN RESISTANCE

Ventromedial hypothalamic lesions in rats can cause hyperphagia and excessive weight gain in association with glucose intolerance, hyperglycaemia, hyperinsulinaemia and hypertriglyceridaemia which are classical manifestations of metabolic syndrome [24–27]. Infusion of norepinephrine plus serotonin into the ventromedial hypothalamus impaired pancreatic islet function in as much as ventromedial hypothalamic norepinephrine and serotonin levels are elevated in hyperinsulinaemic and insulin resistant animals [28]. Treatment with insulin restored the levels of neurotransmitters in the hypothalamus. It is possible that ventromedial hypothalamic dysfunction can impair pancreatic beta cell function and induce metabolic abnormalities characteristic of insulin resistance and 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 rat obese (ob) gene is upregulated even in non-genetic obesity [26–31]. The hyperphagic and obese ventromedial hypothalamic lesioned rats may have suppressed splenic natural killer cell activity which predisposes proinflammatory responses [31]. These responses may become worst if there is underlying deficiency of long-chain PUFAs in the hypothalamus and other vulnerable parts of the brain. The brain cells generate interferon-alpha, IL-1, IL-2 and TNF-alpha in response to various stresses [32, 33].

INSULIN RESISTANCE AND INSULIN RECEPTORS IN THE BRAIN

Animal studies [34] revealed greater food consumption and food-sensitive obesity with increases in body fat and plasma leptin levels, insulin resistance, hyperinsulinaemia and hypertriglyceridaemia, which are classical manifestations of metabolic syndrome. It seems that a reduction in the number of insulin receptors, poor function of insulin receptors and insulin deficiency or resistance in the brain result in the development of metabolic syndrome, despite normal pancreatic beta cells. This experiment also showed that intraventricular injection of insulin inhibited food intake in the animals [34]. However, neuropeptide Y levels in the paraventricular nucleus on food deprivation, which returns to the control range after insulin administration, without altering blood glucose levels. Similar changes were observed on peripheral insulin administration.

As mentioned earlier, the brain is rich in insulin receptors, particularly in the hypothalamus, pituitary and olfactory bulb [36, 37]. There is an increase in neuropeptide Y levels in the paraventricular nucleus on food deprivation, which returns to the control range after insulin administration, without altering blood glucose levels. Similar changes were observed on peripheral insulin administration.

Sahu et al. [38] showed that insulin and insulin-like growth factor-II (IGF-II) reduced the release of neuropeptide Y in a dose-dependent manner 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 [38]. As neuropeptide Y is a potent orexigenic signal and because insulin and IGF-II reduce hypothalamic neuropeptide Y levels, it is possible that the optimal amount of insulin, insulin receptors and IGF-II in the brain might decrease appetite and food intake, resulting in modulation of insulin resistance. One experiment [39], in rats fed ad libitum, administered glucose or insulin caused increased extracellular acetylcholine in the amygdala. Acetylcholine is known to reduce dopamine secretion [40] and low levels of dopamine may enhance appetite [41]. Acetylcholine also prevents the synthesis and release of TNF-alpha in vitro and in vivo [42]. Therefore, it is possible that one major function of insulin, IGF-II and acetylcholine in the brain is to protect neurones from the death signals of TNF-alpha, IL-1, IL-2 and IL-6 and increase the release of anti-inflammatory cytokines.

PUFAs AND INSULIN RECEPTORS

One group [43] has described that adequate amounts of arachidonic acid and DHA are necessary for the 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 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 membranes and neural tissue. A decreased supply of these fatty acids in infant formula milk based on vegetable oil may result in suboptimal
neural development and dysfunction due to decreased brain PUFA content [43, 44]. 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 energy metabolism in the cerebral cortex by stimulating glucose uptake by the cortical astrocytes [45]. Increased availability of glucose increases acetylcholine release in the brain [46]. It is clear that arachidonic acid enhances acetylcholine release by enhancing glucose uptake in the brain. Similarly, DHA is known to enhance cerebral acetylcholine levels and improve learning ability in rats [47]. Obesity is an important component of metabolic syndrome, which may be associated with fewer dopamine receptors and lower dopamine levels [41]. Acetylcholine interacts with dopamine receptors in the hippocampus [48] 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 insulin receptors 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 [19]. Insulin and IGF-I can prevent TNF-alpha-induced neuronal damage [21, 22].

An excess of linoleic acid may enhance oxidative stress, whereas insulin and long-chain PUFAs regulate superoxide anion generation, which may increase the production of endothelial nitric oxide (eNO) [49-52]. NO can quench free radicals and is anti-inflammatory [53]. There is some evidence that IGF-I and possibly insulin may increase acetylcholine release from the cortical slices [54] which has anti-inflammatory activity and is a potent stimulator of eNO synthesis [55]. It is possible to conclude that insulin, IGF-I, acetylcholine and long-chain PUFAs inhibit the production of TNF-alpha and augment the synthesis of eNO. Acetylcholine and eNO are neuroprotective as well as interact with other neurotransmitters. It is possible that the most important function of PUFAs is to ensure an adequate number of insulin receptors in the brain. If an adequate amount of PUFAs is not incorporated in the neuronal cell membranes during fetal development and infancy, it may cause a defect in the expression or function of insulin receptors resulting in 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 in improvement in insulin sensitivity [56–60].

CLINICAL EVIDENCE ON INSULIN RESISTANCE AND PUFA S

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 [61, 62]. It is possible that the presence of long-chain PUFAs in breast milk may be the cause of the negative association between breast feeding and insulin resistance and type 2 diabetes (metabolic syndrome). The decline in breast feeding may also be the cause of a recent increase in the prevalence of type 2 diabetes, hypertension and CAD in certain populations such as south Asians [8–10]. In south Asians, fetal undernutrition and a greater prevalence of metabolic syndrome compared with Caucasians and Chinese have also been described [63–65]. In Pima Indians [66, 67], bottle-fed children had a significantly greater prevalence of type 2 diabetes compared with breast-fed children. In one study [61], bottle-fed subjects showed a higher mean 2-hour plasma glucose level after an oral glucose tolerance test compared with breast-fed subjects. In another study [62], 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 [56]. As human breast milk is rich in long-chain PUFAs, gamma-linolenic acid, dihomo-gamma-linolenic acid, arachidonic acid, EPA and DHA, the beneficial effects of breast feeding in the prevention of metabolic syndrome may be attributed to these fatty acids.

One study [68] showed a significant association between insulin secretion and action and arachidonic acid. In another study [69], 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 [56]. 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 [70]. It seems that the major actions of PUFAs are directed to the prevention of insulin resistance, hypertension, and type 2 diabetes and may be least effective when these diseases are established. This finding also explains the association between breast feeding and the decline in the incidences of insulin resistance, diabetes and hypertension [60, 62, 66, 71, 72]. However, in patients with CAD, the role of n-3 fatty acids has been found to be useful in many studies [73–75], although the effects on brain function were not reported in these studies.

In infants, especially those who are pre-term, the synthesis of long-chain PUFAs from alpha-linolenic acid and linoleic acid is inadequate in the early stages of life [76–78]. 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 maintenance of insulin receptors due to inadequate PUFAs are low and the concentrations of proinflammatory cytokines TNF-alpha, responsible for neurodegeneration, would be greater [79]. 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 the ventromedial hypothalamus resulting in the development of insulin resistance and metabolic syndrome. Weisinger et al. [80] also showed that a deficiency of DHA in the perinatal period can cause hypertension in later life, despite the deficiency being repaired with this fatty acid in animals subsequently. As hypertension is a manifestation of metabolic syndrome, DHA deficiency causing insulin resistance and metabolic syndrome is a good possibility. Energy intake is quite essential in the development of obesity, which is an important determinant of insulin resistance and metabolic syndrome. As PUFAs can regulate food intake, it is possible that long-chain PUFA consumption may influence the development of obesity and type 2 diabetes, which are components of insulin resistance syndrome. Long-chain PUFAs can modulate the endogenous lipids N-aceyl-ethanolamine (anandamide) and 2-acyl-glycerols, the ligands of canna-Binoid receptors that are important for food intake. 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 breast milk to fine tune their beneficial actions by their ability to influence cell membrane fluidity, expression of receptors on the membranes and subsequent post-receptor events [72]. As breast milk and long-chain PUFAs can independently modulate obesity, insulin resistance, hypertension, diabetes mellitus and CAD (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 [56, 62, 67, 71, 72, 81, 82]. It is not clear where and how much long-chain PUFAs should be available to prevent the development of metabolic syndrome. Apart from the 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 PUFA administration (through breast milk or mother’s nutrition) during the critical periods of growth (third
trimester to second year post-term) accumulates in the special areas of the brain as well as in vessel walls including the endothelium, heart, 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 [83], erythrocyte phospholipid arachidonic acid and DHA levels of the umbilical cord vein were significantly lower in women with gestational diabetes compared with healthy pregnant subjects. This study also showed that glycosylated haemoglobin in mothers was inversely associated with fetal erythrocyte DHA and arachidonic acid in gestational diabetes mellitus. It may be due to fetal impairment in the 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 [84], a high fat, low carbohydrate diet decreased the ability of insulin to modulate endogenous glucose production. A further study [85] showed that substituting dietary saturated fat for monounsaturated fat impaired insulin sensitivity in healthy subjects. In a long-term follow-up study [86, 87], long-chain PUFAs (especially n-3) caused a 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 in a decline in the incidence of metabolic syndrome [88–90]. One experimental study [91] further supported this view and showed a decrease in the ratio of DHA to EPA as a result of low delta-5-desaturase activity in hepatic microsomes of retarded offspring in conjunction with higher fasting plasma insulin levels. It seems that the origin of arachidonic acid in breast milk is neither due to the conversion of linoleic acid nor is it derived from direct intestinal absorption in lactating women and animals; maternal body stores could be the major sources of linoleic acid and arachidonic acid in breast milk. It is important, therefore, to provide long-chain PUFAs to women from external sources to maintain their body stores [92]. This strategy would be useful for the fetus during pregnancy for the development of insulin receptors and the hypothalamus to prevent insulin resistance. There is a need to provide adequate amounts of PUFAs to infants from birth to 2 years post-term, which is the critical period of brain and somatic growth [93]. As the brain can produce neurones at any age, it may be useful to supply PUFAs in later life for the prevention of metabolic syndrome [94]. To determine whether the 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 [95]. The results revealed that 67 children in the PUFA group (64% of the original) and 76 in the non-supplementation group (60%) were enrolled into the follow-up study. The PUFA group had a significantly lower mean blood pressure, systolic (-3.0 mmHg, 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, acupuncture, psychological states or yogic exercises might influence inflammatory or immunological diseases [96, 97]. Wang and colleagues [96] showed that activation of nicotinic acetylcholine receptors on macrophages reduces the release of proinflammatory cytokines TNF-alpha and IL-1 and IL-6, induced by endotoxin lipopolysaccharide. There is direct evidence that vagal nerve stimulation, acting through these receptors, can reduce inflammatory responses. As long-chain PUFAs can stimulate vagal nerve-induced acetylcholine levels, it is possible that these fatty acids might influence nicotinic acetylcholine receptors and may be beneficial in lung disease.
**MUFA’s AND INSULIN RESISTANCE**

Apart from n-3 fatty acids, MUFA’s have been found to be protective against insulin resistance [2–5]. MUFA-rich diets have the potency to improve lipid profiles and may also have antioxidant properties. Ryan *et al.* [97] examined the effect of an oleic acid-rich diet on insulin resistance and endothelium-dependent vasoreactivity in type 2 diabetes. They found endothelium-dependent flow-mediated vasodilatation significantly greater on the oleic acid-rich diet. The MUFA-rich diet reduced insulin resistance and restored endothelium-dependent vasodilatation and is probably responsible for the anti-atherogenic benefits of a Mediterranean-type diet. Riccardi and Rivellese [98] showed, in a large multicentre intervention study in healthy individuals given either a high saturated fat or a high monounsaturated fat diet for 3 months, that a high MUFA content in the diet significantly improved insulin sensitivity compared with a high saturated fat diet. Similar results were observed in the KANWU study in Sweden. This study included 162 healthy subjects chosen at random to receive a controlled isoenergetic diet for 3 months, containing either a high proportion of saturated fat (SAFA diet) or monounsaturated (MUFA diet) fatty acids. Insulin sensitivity was significantly impaired on the SAFA diet (−10%, *p* = 0.03) but improved in the MUFA diet (+2%, not significant) (*p* = 0.05 for the difference between diets). Insulin secretion was not affected [85]. In contrast, the findings of Lovejoy *et al.* [99] showed that dietary fatty acid composition significantly influenced oxidation but did not impact insulin sensitivity or secretion in lean individuals. In a cross-sectional study (Pizarra), anthropometrical data were measured in 538 subjects, aged 18–65 years, selected randomly from the municipal census of Pizarra (Spain). An oral glucose tolerance test was given to all subjects and measurements of glycaemia, insulinaemia and the proportion of fatty acids in plasma phospholipids were made. Insulin resistance was estimated by homeostasis model assessment. The strength of association between variables was measured by calculating the odds ratio from logistic models, and the relationships were measured by linear correlation coefficients. Insulin resistance was significantly less in people who used olive oil compared with those who used sunflower oil or a mixture. Statistical significance remained in the group of people with normal oral glucose tolerance test after adjusting for obesity. In the whole sample, insulin resistance correlated negatively with the concentration of oleic acid (*r* = −0.11; *p* = 0.02) and positively with that of linoleic acid (*r* = 0.10; *p* = 0.02) from the cooking oil. The risk of having raised insulin resistance was significantly lower in people who consumed olive oil, either alone (odds ratio = 0.50) or mixed (odds ratio = 0.52) compared with those who consumed only sunflower oil. The association between the intake of oleic acid, the composition of oleic acid in plasma phospholipids and peripheral insulin action was confirmed [100].

Emerging data suggest that diets higher in unsaturated fatty acids, particularly MUFA’s, have several advantages over high carbohydrate intakes. This advantage appears to hold, particularly for populations having a high prevalence of insulin resistance, such as the US population. If the US public was to modify its eating habits in the direction of better weight control and more exercise, higher intakes of carbohydrate might be better tolerated. At the same time, the experience with the Mediterranean population reveals that in healthier populations, diets relatively high in unsaturated fatty acids are well tolerated and are associated with a low prevalence of both coronary heart disease and type 2 diabetes [101].

**ANTIOXIDANTS, MINERALS AND INSULIN RESISTANCE**

Oxidative stress may play a role in the pathophysiology of diabetes and cardiovascular disease, but little is known about the antioxidant status among individuals with metabolic syndrome who are at high risk of developing these conditions. Using data from the Third
National Health and Nutrition Examination Survey (1988–1994), the circulating concentrations of vitamins A, C, and E, retinyl esters, five carotenoids and selenium were compared in 8808 US adults aged ≥ 20 years with and without metabolic syndrome. After adjusting for age, sex, race or ethnicity, education, smoking status, physical activity, fruit and vegetable intake, and vitamin or mineral use, the participants with metabolic syndrome had significantly lower concentrations of retinyl esters, vitamin C and carotenoids, except lycopene. With additional adjustment for serum lipid concentrations, vitamin E concentrations were significantly lower in participants with metabolic syndrome than those without the syndrome. Retinol concentrations were similar between the two groups. After excluding participants with diabetes, the results were very similar. The consumption of fruits and vegetables was also lower among people with metabolic syndrome. Adults with metabolic syndrome have suboptimal concentrations of several antioxidants, which may partially explain their increased risk for diabetes and cardiovascular disease [102]. The altered plasma statuses of selected minerals (calcium, magnesium, copper, zinc) have been noted in a cluster of insulin resistance syndromes, including hypertension and diabetes mellitus. In one study [103], the differences in plasma values of these minerals in hypertensive men with and without insulin resistance, as evaluated by an insulin suppression test, were investigated. The results showed that the plasma values of the determined minerals at fasting, 2 hours after an oral glucose challenge, and after the insulin suppression test did not markedly differ between hypertensive subjects with and without insulin resistance. However, hypertensive subjects had significantly lower plasma calcium values at fasting and 2 hours after an oral glucose load, and higher fasting plasma zinc values, than normotensive controls. Hypertensive subjects also had higher steady-state plasma glucose values, higher zinc and lower magnesium and copper values after the insulin suppression test, when compared with controls. The study suggests that an altered plasma status of selected minerals in hypertension cannot be totally ascribed to the co-exhibition of insulin resistance.

Singh et al. [104] found that lower consumption of dietary zinc and low serum zinc levels were associated with an increased prevalence of CAD and diabetes and several of their associated risk factors, including hypertension, hypertriglyceridaemia and other factors suggestive of mild insulin resistance.

INSULIN RESISTANCE, METABOLIC SYNDROME AND CIRCADIAN RHYTHM

The rhythm of everyday 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 dark, and under the weak influence of plasma melatonin levels secreted by the pineal gland [105–107]. It is possible that long-chain PUFA content, especially DHA and EPA, of the neurones situated around the suprachiasmatic nucleus and pineal gland may be important in the pathogenesis of the circadian rhythm of cardiac events and insulin resistance. A low content of long-chain PUFAs can enhance the sensitivity of the suprachiasmatic nucleus to light, leading to a greater surge of catecholamines, resulting in excess formation of TNF-alpha, IL-1, IL-2 and IL-6 which are proinflammatory cytokines. These cytokines are known to damage various target organs responsible for insulin resistance and metabolic syndrome. A circadian cycle is present in every cell which is controlled by neurotransmitters in the autonomic system including our neuroendocrine time structures [105, 106]. Triggering of the suprachiasmatic nucleus due to a deficiency of long-chain PUFAs and other environmental factors may activate sensors, receptors and hormones (the pineal gland, pituitary functions and adrenal secretions) resulting in an increase in adverse effects on circadian variations, heart rate variability and blood pressure variability [105–107]. There is evidence that saturated and total fat intake may enhance sympathetic
activity with an increase in catecholamines, cortisol, serotonin, insulin and oxidative stress, whereas treatment with omega-3 fatty acids can inhibit sympathetic activity by enhancing parasympathetic activity leading to increased secretion of acetylcholine in the hippocampus [105] which may blunt the release of proinflammatory cytokines and enhance the release of anti-inflammatory cytokines. It is possible that n-3 fatty acids incorporate in the phospholipids of the cell membrane and stabilize the excitatory neurones, cardiomyocytes and arterial smooth muscle as well as endothelial cells [108, 109].

Existing studies indicate that increased physical activity may be associated with lower concentrations of insulin, proinflammatory cytokines TNF-alpha and IL-1 and IL-6 and insulin resistance which may have a beneficial effect on the insulin receptors and the hypothalamus. Physical inactivity is an important risk factor for insulin resistance and metabolic syndrome and regular exercise is a most powerful tool in its management. Exercise training as part of a comprehensive cardiac rehabilitation programme has been shown to improve morbidity and mortality rates in patients after myocardial infarction. It is possible that the benefits of cardiac rehabilitation may be achieved through an altered cardiovascular autonomic tone, improvement in the functioning of insulin receptors and the ventromedial hypothalamus inhibiting insulin resistance. Exercise training has a beneficial effect on autonomic tone as well as on various components of insulin resistance and metabolic syndrome. A diet rich in n-3 fatty acids, MUFAs, zinc, chromium and phytochemicals, such as that advised in the Indo-Mediterranean diet heart study (400 g day\(^{-1}\) of fruits, vegetables and nuts and 400 g day\(^{-1}\) of whole grains) may be protective against insulin resistance syndrome [9, 74].

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