

## Review Article

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# Diet & insulin resistance: A review & Asian Indian perspective

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**Insulin resistance is associated with type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD). These abnormalities have been aggravated because of imbalanced and excess nutrition in developed countries, and rapid nutritional and lifestyle transition occurring in developing countries. This review presents evidence linking dietary nutrients with insulin resistance and its metabolic correlates, and also describes these issues from a Asian Indians and South Asian perspective. Despite possible influences from genetic and perinatal factors, diet and physical activity are likely to have greater and often overriding influence in pathogenesis of the insulin resistance, the metabolic syndrome, and T2DM. In animal studies, a link has been established between dietary nutrients and insulin resistance. However, in human studies evidence is not as strong as in animals. Data suggest that dietary  $\omega$ -3 polyunsaturated fatty acids (PUFAs) improve lipid profile and may have beneficial effect on insulin resistance. Dietary saturated fatty acids intake is positively associated with insulin resistance. Also, low glycaemic index foods and whole grain intake decrease insulin resistance. Importantly, high carbohydrate diets increase plasma triglycerides, cause hyperinsulinaemia and decreases low-density lipoprotein cholesterol. Among micronutrients, high magnesium and calcium intake have been reported to decrease insulin resistance. High intake of dietary carbohydrate and  $\omega$ -6 PUFAs, low intake of  $\omega$ -3 PUFAs and fiber, and high  $\omega$ -6/ $\omega$ -3 PUFAs ratio have been reported in South Asians. Our recent investigations have shown that increased dietary  $\omega$ -6 PUFAs and saturated fat intake are significantly associated with fasting hyperinsulinaemia and sub-clinical inflammation, respectively. Such imbalanced diets contribute to high prevalence of insulin resistance, the metabolic syndrome and T2DM in South Asians and Asian Indians.**

**Key words** Asian Indian - dietary carbohydrates - dietary fats - dietary micronutrients – dyslipidaemia - insulin resistance - type 2 diabetes mellitus

## Introduction

Insulin resistance is associated with type 2 diabetes mellitus (T2DM), cardiovascular diseases (CVD), both independently and in association with the insulin resistance syndrome<sup>1</sup>. Decreased insulin sensitivity has been documented in those known to be at risk for

T2DM, such as normoglycaemic first-degree relatives of patients with T2DM, or women with history of gestational diabetes<sup>2,3</sup>. It is now well established that generalized obesity and abdominal obesity (excess subcutaneous and intra-abdominal fat) are associated with insulin resistance<sup>4</sup>. Other important factors

contributing to insulin resistance include accumulation of hepatic fat and intra-myocellular lipids, both of which can exist independent of generalized adiposity<sup>5</sup>.

In most people with T2DM, insulin resistance is generally present for many years before the diagnosis<sup>6,7</sup>. Despite possible influences from genetic and perinatal factors, diet and physical activity are likely to have greater and often overriding influence in pathogenesis of the insulin resistance syndrome and T2DM.

This review aims to critically analyse influence of dietary nutrients on the insulin resistance from PubMed (1966-August 2007). A manual search of the relevant quoted references was also carried out from the retrieved articles.

### Dietary fats and insulin resistance

*1. Dietary polyunsaturated fatty acids (PUFAs):* An impressive body of evidence has established the link between dietary lipids, membrane lipids and insulin resistance in animal studies. An elegant study by Storlein *et al*<sup>8</sup> showed that replacement of as little as 6 per cent  $\omega$ -6 PUFAs (safflower oil) with long chain (LC)  $\omega$ -3 PUFAs (fish oil) was able to prevent the development of insulin resistance. Further,  $\omega$ -6 PUFAs rich oil feeding intensifies insulin resistance when compared with feeding LC  $\omega$ -3 PUFAs<sup>9,10</sup>. LC  $\omega$ -3 PUFAs supplementation can improve insulin action, reversing the adverse effects of saturated fatty acids (SFAs) and sucrose<sup>11,12</sup>. However in human, studies have not shown strong evidence as in rodents.

Protective effect of fish intake on the development of insulin resistance has been reported in prospective epidemiological studies<sup>13,14</sup>. However, there are no consistent reports of improvements in insulin action in response to LC  $\omega$ -3 PUFAs supplementation in dietary intervention studies. The majority of studies have been conducted in patients with T2DM, and it is generally accepted that supplementation with LC  $\omega$ -3 PUFAs does not have a negative effect on the metabolic parameters<sup>11</sup>. Further, LC  $\omega$ -3 PUFAs supplementation may improve insulin sensitivity in patients with impaired glucose tolerance<sup>15</sup> and in patients with T2DM<sup>16</sup>. However, impact of LC  $\omega$ -3 PUFAs supplementation on metabolic parameters in healthy volunteers has not been investigated adequately. Some investigators have reported an improvement in insulin sensitivity in response to  $\omega$ -3 PUFAs supplementation<sup>16</sup>, while others have observed no change<sup>17,18</sup>.

Long-term intervention studies are few in number and have also failed to show significant improvements in insulin sensitivity in healthy subjects and in patients with T2DM<sup>19</sup>. For example, a 6-months randomized controlled trial in patients with T2DM evaluated the effects of a moderate supplementation of fish oil (2.7 g/day for the first 2 months and 1.7 g/day for the remaining 4) on glucose control and lipid metabolism<sup>19</sup>. Fish oils had a significant serum triglyceride-lowering effect, without any change in overall glucose control and no change in peripheral glucose utilization measured by hyperinsulinaemic clamp<sup>20</sup>. Recently, Griffin *et al*<sup>21</sup> evaluated the effect of  $\omega$ -6/ $\omega$ -3 PUFAs ratio on insulin sensitivity on 258 subjects (aged 45-70 yr) in a 6-month randomized control trial. These investigators showed that decreasing  $\omega$ -6/ $\omega$ -3 PUFAs ratio did not influence insulin sensitivity although lipid profile improved with increased intake of LC  $\omega$ -3 PUFAs.

Postulated mechanisms for the putative beneficial effects of LC  $\omega$ -3 PUFAs on insulin action include beneficial alterations in the physical properties of the cellular membranes, such as increased fluidity<sup>22,23</sup>. LC  $\omega$ -3 PUFAs supplementation causes a marked increase in the eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) content with a concomitant reduction in arachidonic acid in the membranes of cells, especially in the membranes of platelets, erythrocytes, neutrophils, monocytes and liver cells<sup>24,25</sup>. Also,  $\omega$ -6 PUFAs enriched diet inhibits EPA incorporation in the membrane<sup>26</sup>. Enrichment in tissue levels of LC  $\omega$ -3 PUFAs in skeletal muscle is associated with enhanced insulin sensitivity<sup>27</sup> and a high  $\omega$ -6/ $\omega$ -3 PUFAs ratio in muscle membrane lipids is associated with increased fasting insulin levels<sup>11</sup>.

Inflammation and oxidative stress could be underlying mechanisms important for the development of insulin resistance<sup>28</sup>. LC  $\omega$ -3 PUFAs are independently associated with low levels of pro-inflammatory interleukin-6 (IL-6), IL-1ra, tumour necrosis factor- $\alpha$  (TNF $\alpha$ ), C-reactive protein (CRP)- and high levels of anti-inflammatory cytokines [soluble IL-6r, IL-10, tumour growth factor- $\alpha$  (TGF $\alpha$ )]<sup>29</sup>. The  $\omega$ -6/ $\omega$ -3 PUFAs ratio is a strong negative correlate of IL-10. Further, Mediterranean diets lowers ratio of  $\omega$ -6/ $\omega$ -3 PUFAs in serum phospholipids, the number of platelets and leukocytes and vascular endothelial growth factor in healthy subjects<sup>30</sup>.

Fish oils increase plasma adiponectin concentrations<sup>31</sup>, which has been shown to reverse

insulin resistance in rodents in part by increasing hepatic insulin sensitivity<sup>32,33</sup>. Several studies suggest that LC  $\omega$ -3 PUFAs serve as important mediators of gene expression, working via the peroxisome proliferator-activated receptors which control the expressions of the genes involved in lipid and glucose metabolism and adipogenesis<sup>34,35</sup>. Experimental studies have shown that fish oils could downregulate the hepatic mRNA level of the sterol regulatory element-binding protein-1 which also controls several other lipogenic genes<sup>36-37</sup>. Studies have shown that carbohydrate-responsive element-binding protein (ChREBP) is central for the co-ordinated inhibition of glycolytic and lipogenic genes by PUFAs<sup>38</sup>. EPA and DHA suppress ChREBP activity by increasing its mRNA decay and by altering ChREBP protein translocation from cytosol to nucleus both in primary cultures of hepatocytes and in liver *in vivo*. Further, increased dietary LC  $\omega$ -3 PUFAs may alter the binding affinity of the insulin receptor and improve glucose transport into cells via glucose transporters<sup>39</sup>. Importantly,  $\omega$ -3 PUFAs are potent inhibitors of very low density lipoprotein (VLDL) synthesis<sup>40</sup>. Since VLDL-triglycerides are important energy source in peripheral tissues, a mechanism based on fuel switching with reduced fatty acids and increased glucose utilization (the glucose-fatty acid cycle of Randle) cannot be ignored.

Overall, studies have shown that dietary  $\omega$ -3 PUFAs increase EPA and DHA content of phospholipids membrane, improve lipid profile and have either a beneficial or no effect on insulin sensitivity.

2. *Dietary saturated fatty acids (SFAs)*: Intake of SFAs is a significant independent predictor of fasting and postprandial insulin concentrations<sup>41,42</sup>. Parker *et al*<sup>41</sup> showed that if SFAs as a percentage of total energy are to decrease from 14 to 8 per cent, there would be an 18 per cent decrease in fasting insulin levels and a 25 per cent decrease in postprandial insulin levels. Vessby *et al*<sup>20</sup> investigated SFAs-rich diet and a diet containing high proportion of monounsaturated fatty acids (MUFAs) for three months in 162 healthy subjects, and showed that SFA-rich diet impairs insulin sensitivity. Isocaloric substitution of PUFAs for SFAs improved insulin sensitivity and resulted in decrease in subcutaneous abdominal fat area without any change in weight, waist-hip ratio and percentage body fat<sup>43</sup>.

In healthy men, glucose-stimulated insulin secretion is increased after ingestion of SFAs and this may be due to a rise in plasma gastric inhibitory

polypeptide<sup>44</sup>. Healthy volunteers exhibited decrease binding of insulin to monocyte insulin receptors when fed a high calorie diet rich in SFAs<sup>45</sup>. Feeding a diet with a high PUFAs/SFAs ratio to patients with T2DM is associated with higher insulin binding to its receptor compared with to those on a diet with lower ratio of the same<sup>46</sup>.

In humans, insulin resistance directly correlates with increased SFAs in skeletal muscle triacylglycerides<sup>47</sup>. In C<sub>2</sub>C<sub>12</sub> skeletal muscle cells, palmitate has been shown to reduce insulin-stimulated glycogen synthesis through the inhibition of glycogen synthase kinase-3 and protein kinase B phosphorylation<sup>48</sup>. Ceramide, a derivative of palmitate, has been proposed to be responsible for these inhibitory effects and the induction of insulin resistance<sup>48</sup>. Diacylglycerol accumulation from SFAs has been shown to reduce glucose uptake via desensitization of insulin stimulation in human skeletal muscle cells<sup>49</sup>. Further, prolonged *in vitro* exposure of islets to above physiological concentrations of palmitate decreases the insulin content and impairs insulin gene expression in the presence of elevated glucose levels<sup>50-52</sup>. This seems to be mediated by a decreased insulin gene promoter activity<sup>51</sup> and decreased binding of the transcription factor, pancreas duodenum homeobox-1, to the insulin gene in islets<sup>52</sup>. Elevated palmitate concentrations can affect cellular signaling by inhibiting insulin receptor or the insulin receptor substrate-1 phosphorylation<sup>53</sup> and Akt activation<sup>48,54</sup>. Palmitate has also been shown to induce IL-6 mRNA expression<sup>55</sup> and result in downregulation of glucose transporter 4 (GLUT4) by protein kinase C and nuclear factor- $\kappa$ B-dependent mechanism<sup>56</sup>.

Overall intake of dietary SFAs is positively related to insulin resistance. Replacing SFAs with MUFAs or PUFAs in dietary fat may be a useful dietary intervention to prevent metabolic deterioration.

3. *Dietary mono unsaturated fatty acids (MUFAs)*: Garg *et al*<sup>57</sup> investigated high carbohydrate diet (65% carbohydrate, 25% fat) and high MUFAs diet (50% fat of which 33% MUFAs, 35% carbohydrate), in patients with T2DM and showed that MUFAs-rich diet lowered mean plasma glucose levels and insulin resistance. Further, MUFAs-rich diets lowered plasma triacylglycerol (19%), total cholesterol (3%), VLDL-C (22%) and increased HDL-C (4%) although LDL-C did not differ significantly between two diets<sup>58</sup>. A meta-analysis of randomized trials using isoenergetic high MUFAs diets in patients with T2DM showed that these diets improve lipoprotein and glycemic profiles<sup>58</sup>.

It has been pointed out that the improvement with high MUFAs diets may not be related to changes in insulin sensitivity but due to a reduction in the carbohydrate load, which T2DM subjects may not be able to handle readily because of severe insulin resistance and  $\beta$ -cell defect<sup>58</sup>. Folsom *et al*<sup>59</sup> in a cross-sectional study of 4304 non-diabetic subjects showed that fasting insulin concentration was inversely associated with MUFAs percentage and positively associated with SFAs percentage in platelet phospholipids. Short-term intervention studies in healthy volunteers have shown that the isocaloric substitution of MUFAs for SFAs<sup>60</sup>, or even substituting MUFAs for carbohydrates<sup>61</sup>, can have positive effects on insulin sensitivity. Similar results were obtained in a 3-month trial that evaluated insulin sensitivity in healthy volunteers receiving three diets varying in fatty acid composition ( $\omega$ -3 PUFAs vs. MUFAs vs. SFAs). MUFAs-enriched diet resulted in significant increases in insulin sensitivity, and this effect was greater when the total amount of fat was modest (<37% of calories)<sup>20</sup>. On the contrary, some investigators have not found beneficial effect of high MUFAs diet on insulin sensitivity<sup>62,63</sup>.

There could be several mechanisms for the increase in insulin sensitivity induced by MUFAs-rich diets. The MUFAs may have a different effect on gastric emptying. Soriguer *et al*<sup>64</sup> showed that rats fed with MUFAs have a greater amount of fat in their feces and a lower calorie balance than rats fed with SFAs or with  $\omega$ -6 or  $\omega$ -3 PUFAs, an effect which could be mediated by glucagon-like-peptide 1 (GLP-1) inhibition of gastric emptying<sup>65</sup>. GLP-1 is secreted by intestinal L cells in response to a meal and boosts the secretion of insulin stimulated by glucose in a dose-dependent fashion<sup>66</sup>. A study in healthy subjects and in persons with T2DM, has shown that levels of GLP-1 are increased more by dietary MUFAs than by dietary SFAs<sup>67</sup>, and that the greater postprandial clearance of an oral overload of MUFAs-rich fats is associated with a greater increase in postprandial incretins such as GLP-1 or gastric inhibitory polypeptide. Tinahones *et al*<sup>68</sup> showed that postprandial hypertriglyceridaemia is independently associated with  $\beta$ -cell function in the metabolic syndrome, with numerous studies demonstrating that the type of dietary fat influences the plasma clearance of postprandial lipaemia<sup>67</sup>. It has been shown that dietary proportion of MUFAs,  $\omega$ -3 PUFAs, and  $\omega$ -6 PUFAs determine  $\beta$ -cell function<sup>69</sup>. Also, MUFAs increase basal glucose uptake by inducing an increase in GLUT1 and GLUT4 in the cell

membrane<sup>70</sup>. A recent study suggested that an isocaloric MUFAs-rich diet prevented central fat redistribution and the postprandial decrease in peripheral adiponectin gene expression and insulin resistance induced by a carbohydrate-rich diet in insulin resistant subjects<sup>71</sup>.

Overall, high MUFAs diets have shown beneficial effect in management of T2DM but its influence on insulin resistance, although appears beneficial, is still inconclusive.

4. *Dietary trans fatty acids (TFAs)*: Dietary TFAs intake has been found to be associated with dyslipidaemia and increase risk of T2DM and CVD, but the relationship between dietary TFAs and insulin resistance has been poorly investigated. Studies in patients with T2DM have shown an elevated postprandial insulin response with TFAs-rich diet as compared to cis-MUFAs-rich diet<sup>72</sup>. Lichtenstein *et al*<sup>73</sup> investigated the metabolic effect of TFAs in 36 overweight mildly hypercholesterolaemic subjects in a randomized cross-over study. These investigators showed no dose-response effect of TFAs on fasting insulin concentrations. However, the butter-rich diet and the diet high in shortening margarine (contained more 18:2 trans) produced the highest insulin levels among the three TFA-enriched diets. The data regarding dietary influence of TFAs on insulin resistance in healthy subjects are limited. Louheranta *et al*<sup>74</sup> investigated the effect of TFAs on insulin sensitivity in 14 healthy young Finnish women, and showed that there were no differences between TFAs-enriched diet and MUFAs-enriched diets on insulin sensitivity, although fasting insulin concentrations tended to be higher after TFAs-enriched diet. Lovejoy *et al*<sup>75</sup> investigated diets rich in SFAs (9% C16:0), MUFAs (9% C18:1 cis) and TFAs (9% C18:1 trans) in a randomized cross-over design in 25 healthy subjects and showed that there were no significant difference between diets on insulin sensitivity. In the population-based prospective study on 84204 women Salmeron *et al*<sup>76</sup> showed that a 2 per cent increase in dietary trans fatty acids increased the risk of developing type 2 diabetes by 40 per cent (OR-1.39). Overall, limited data suggest that dietary TFAs intake, although associated with dyslipidaemia and increase risk of T2DM and CVD, may not affect insulin sensitivity especially in healthy individuals<sup>77</sup>.

*Conjugated linoleic acid (CLA)*: CLA is a mixture of positional and geometric isomers of LA (18:2n-6) commonly found in beef, lamb and dairy products. The most abundant isomer of CLA in nature is the

cis-9, trans-11 (c9t11) isomer. Commercially available CLA is usually a 1:1 mixture of c9t11 and trans-10, cis-12 (t10c12) isomers with other isomers as minor components. Data suggest that either of bioactive isomer c9t11 and t10c12, increases insulin resistance and mixture of both isomers does not<sup>78,79</sup>. Further, the supplementation of t10c12 was found to increase CRP, a marker of inflammation, whereas the isomeric mixture did not. Recently, Syvertsen *et al*<sup>80</sup> evaluated the effect of CLA (as a commercial preparation containing a mixture of c9t11 and t10c12) on insulin sensitivity using euglycaemic hyperinsulinaemic clamp method in 118 healthy overweight and obese subjects in a randomized double-blind placebo controlled trial for 6 months. These investigators showed that CLA mixture had no deleterious effect on either glucose metabolism or insulin resistance. Further, in several animal and *in vitro* studies, CLAs have shown beneficial effects on, atherosclerosis<sup>81</sup>, immunity<sup>82</sup> and cancer<sup>83</sup>. In addition, adiposity was reported to be reduced with CLA use in animal studies<sup>84,85</sup> including reduction in adipocytes cell size<sup>84</sup>, decreased omental<sup>84</sup> and retroperitoneal adipose tissue depots<sup>86</sup>.

Overall, limited data suggest that dietary TFAs intake, although associated with dyslipidaemia and increase risk of T2DM and CVD, may not affect insulin sensitivity especially in healthy individuals.

### Dietary carbohydrate intake and insulin resistance

Although dietary fat influence on insulin resistance and T2DM is focus of investigators, the amount, type and rate of digestion of dietary carbohydrate may be the primary determinants of postprandial glucose levels and insulin response.

1. *Sucrose/fructose*: Studies by Beltsville group and by others<sup>87,88</sup> showed that high sucrose diet is associated with high fasting insulin concentrations. Beck-Nielsen *et al*<sup>89</sup> found a 25 per cent decrease in insulin sensitivity in a fructose-supplemented group compared with a glucose-supplemented group. They reported that insulin binding to monocytes was decreased in the fructose fed group. However, it is important to note subjects with hyperinsulinaemia or hypertriglyceridaemia who might be more sensitive to the negative effects of high sucrose/fructose diet on insulin sensitivity have been investigated in these studies.

In the past few decades, consumption of sugar sweetened drinks has increased and higher consumption of such beverages has been reported

to be associated with increased body weight<sup>90,91</sup> and increased risk of T2DM<sup>91,92</sup>. Sugar-sweetened drinks contain large amounts of high fructose corn syrup<sup>93</sup>, which consists of 55 per cent fructose and 45 per cent glucose<sup>94</sup>. The composition of high fructose corn syrup is similar to sucrose<sup>95</sup> and therefore, these added caloric sweeteners should in theory be considered equivalent with respect to their effects on metabolic risk factors. Davis *et al*<sup>96</sup> showed that higher intakes of sugar and sugar-sweetened beverages were associated with lower acute insulin response and disposition index (an index of  $\beta$  cell function) in overweight Latino children. Yoshida *et al*<sup>97</sup> investigated 2500 adults and showed that sugar sweetened drinks were positively associated with fasting insulin and homeostasis model assessment index of insulin resistance (HOMA-IR). Further, in the Framingham Offspring Cohort<sup>98</sup>, the positive associations between the consumption of sugar-sweetened drinks, and fasting insulin and the HOMA-IR remained statistically significant even after adjustment for glycaemic index, indicating that this relationship was not fully explained by the effect of the high glycaemic index of sugar-sweetened drinks. In contrast with these studies, others investigators showed no effect<sup>99,100</sup> or positive effect of high sucrose/fructose diet on insulin sensitivity<sup>101,102</sup>.

Hence, high sucrose/fructose diet increases body weight and risk for T2DM and its influence on insulin sensitivity, although appears deleterious, is still inconclusive.

2. *Low glycaemic index foods*: Clinical utility of low glycaemic index (GI) foods continue to be debated because differences in GI between foods may be lost once these foods are consumed in a mixed meal<sup>103</sup>. A mixed meal consists of several carbohydrate sources, hence the effect of the lower GI component is diluted in proportion to the amount of carbohydrate from other foods.

Prospective studies have shown that consumption of low dietary GI foods is associated with a lower risk of T2DM, suggesting a preventive role of low GI diets<sup>104,105</sup>. A low GI diet improves blood glucose control as manifested by lowered day-long glycaemia, lowered glycosylated haemoglobin concentration and improved glucose tolerance<sup>106</sup>. Frost *et al*<sup>107</sup> showed that 4 wk of a low GI diet tended to reduce the area under the glycaemic response curve in response to oral glucose, and significantly reduced the insulin-response area. Several investigators<sup>98,108</sup> but not all<sup>109,110</sup> have

reported positive association between increased dietary intake of GI diet and insulin resistance. Frost *et al*<sup>111</sup> showed that low GI diet improves *in vitro* insulin responsiveness of adipocytes and improves *in vivo* insulin sensitivity. Further, low GI diet decreases total cholesterol, LDL-C, and plasma triacylglycerol levels<sup>112,113</sup> and increases HDL-C levels<sup>114</sup>.

Available data suggest that a high dietary glycaemic load is associated directly with increased risk of coronary artery disease<sup>115</sup> and type 2 diabetes<sup>106</sup>. Compared with women with high intake of cereal fiber and low dietary glycaemic load, those with low cereal fiber intake and high glycaemic load have 2.5-fold higher risk of diabetes<sup>105</sup>. In the 16 year follow up of the Nurses' Health Study from 1980 including 3300 incident cases of type 2 diabetes the association between high glycaemic load and the risk of developing type 2 diabetes was confirmed<sup>116</sup>. Wolever *et al*<sup>117</sup>, investigated effect of low glycaemic load on postprandial plasma glucose and insulin in 34 subjects with impaired glucose tolerance and showed that reducing the fasting glycaemic load of the diet for 4 months significantly reduces postprandial plasma glucose concentration and plasma insulin.

Wolever & colleagues<sup>118</sup> in their studies in normal, diabetic and hyperlipidaemic subjects showed that low GI diets reduced mean blood glucose concentrations, reduced insulin secretion and serum triglycerides in individuals with hypertriglyceridaemia. Some epidemiologic studies suggested that a low GI diet was associated with reduced risk of developing non-insulin diabetes in men<sup>99</sup> and women<sup>100</sup>. Brand-Miller *et al*<sup>119</sup> have carried out a retrospective meta analysis of randomized controlled clinical trials comparing low and high GI diets in the treatment of T1DM and T2DM. They found that low GI diets globally reduced HbA1C by 0.43 per cent points compared to high GI diets in studies with both T1DM and T2DM subjects.

3. *High vs. low carbohydrate diets*: Until relatively recently, recommended diet contained (as percentages of total calories) approximately 15 per cent protein, 25-30 per cent fat and 55-60 per cent carbohydrate; this approach was aimed at decreasing saturated fat intake. The rationale for this recommendation was that it would help decrease CVD risk by maintaining the lowest possible plasma LDL-C concentrations<sup>119</sup>.

High carbohydrate diets increase plasma triacylglycerols and decrease HDL-C levels<sup>70,120</sup> whereas high fat diets decrease plasma triacylglycerols<sup>120</sup>,

decrease HDL-C<sup>121</sup> and increase LDL-C levels. However, when saturated fat is replaced by MUFAs or PUFAs, LDL-C levels decrease and HDL-C levels change slightly<sup>114</sup>. Nelson *et al*<sup>122</sup> have shown that the effect of increasing dietary fat (22 to 39%) on LDL-C and HDL-C concentrations was the same as long as PUFAs/SFAs ratio,  $\omega$ -3/ $\omega$ -6 PUFAs ratio and MUFAs/total fat ratio were identical. These data are congruous with the results of two large meta-analyses<sup>120,123</sup>, and seem to apply equally well to patients with T2DM<sup>70</sup>. Samaha *et al*<sup>124</sup> showed that severely obese subjects with a high prevalence of T2DM and the metabolic syndrome lost more weight and had greater improvements in the plasma triacylglycerols level and insulin sensitivity on a low carbohydrate diet than those on a low fat diet. Strazinsky *et al*<sup>125</sup>, conducted a study on 14 healthy male to show the effect of low fat and high diet. In this randomized cross-over study of 2-wk period insulin sensitivity was improved and lipoprotein cholesterol fractions (total cholesterol by 21.6%, LDL cholesterol by 25.7%, and HDL-cholesterol by 18%) were significantly reduced in low fat diet. Kasim-Karakas *et al*<sup>126</sup>, published the results of a 4-month, controlled dietary study of 54 postmenopausal women in which dietary fat was decreased step-wise from a habitual intake of 35 to 25 per cent and then to 15 per cent of daily energy. During the initial isoenergetic dietary phases, study personnel prepared all foods and the goal was for the subjects to maintain their body weights. The subjects' mean triacylglycerol concentration rose from 151 to 204 mg/dl with increasing dietary carbohydrate ( $P < 0.05$ ). These findings must be interpreted with caution, since the magnitude of the overall weight loss relative to subjects' severe obesity was small, and it is unclear whether these benefits of a carbohydrate-restricted diet extend beyond six months.

Other dietary modifications like low GI food and increasing fiber intake can help to limit the untoward metabolic consequences of the low-fat/high-carbohydrates diets. However, in a study in which the GI index was varied in low-fat/high-carbohydrates diets<sup>119</sup>, the improvements in daylong plasma glucose and insulin concentrations were also of lesser magnitude than the study in which the carbohydrates intake was reduced and the MUFAs intake increased<sup>127</sup>. Similarly it does not appear that the improvement in daylong plasma glucose, and insulin concentrations and fasting plasma lipid concentrations by increasing fiber intake<sup>128</sup> was as great as when a low-fat/high-

carbohydrates diet was compared with a diet in which MUFAs was increased and carbohydrate decreased<sup>127</sup>.

Hence, it is not clear from the available data whether the clinical utility of increasing the fiber content or decreasing the GI of low-fat/high-carbohydrates diets is preferable to simply replacing saturated fat with unsaturated fat and decreasing carbohydrates intake. In order to resolve this question it is necessary to initiate studies in which these alternatives can be directly compared.

4. *Whole grain intake*: There is good evidence that the whole grain intake lowers prevalence of the metabolic syndrome<sup>102</sup> but not all studies are supportive<sup>129</sup>. Whole grain intake has been shown to improve insulin sensitivity<sup>102</sup>, weight loss, lower total cholesterol and LDL-C levels<sup>130</sup>. The evidence is less consistent for refined-grain intake, with some observational studies reporting a positive association with the metabolic syndrome<sup>130</sup> however, others did not find any adverse effect<sup>109</sup>.

Whole grains contain a number of important constituents, including minerals and trace elements (*e.g.*, magnesium, zinc, and manganese), vitamins (vitamin E), fermentable carbohydrates (dietary fiber, resistant starch, and oligosaccharides), and other compounds (phytoestrogens). Because of the particularly high concentration of these substances in the outer layers of the grain, the nutrient content of grains is reduced when the bran and germ layers are removed during the refining process.

Several mechanisms have been proposed for the effect of whole grains and their constituents on metabolism and physiology<sup>131</sup>. Short-chain fatty acids produced by the fermentation of undigested carbohydrates may lead to enhanced glucose oxidation and insulin clearance. Undigested carbohydrates also decrease intestinal transit time. High viscosity of soluble fiber sources (oats, barley, and rye) delays gastric emptying, and intestinal absorption and may result in lower glucose and insulin responses. Starch structure also affects glucose and insulin responses. In particular, low magnesium concentrations have been related to the development of diabetes<sup>110,111</sup>. Antioxidants may improve insulin action by reducing lipid peroxidation in muscle cell membranes, which would enhance the ability of insulin to bind to its receptor<sup>132</sup>. A protective effect of vitamin E on diabetes incidence may exist within the range of intakes available from food<sup>133</sup>. In addition to the constituents of whole grains, food structure has

been found to be highly influential in determining the glucose and insulin responses to foods; any disruption of the physical or botanical structure increases these responses<sup>131</sup>. A more informative analysis, however, might involve separating the intake of fiber from whole grain from the intake of fiber from other foods, because it has been shown that whole-grain fiber is much more beneficial<sup>134</sup>.

Recently, Kallio *et al*<sup>135</sup> randomly assigned 47 adults with the metabolic syndrome to a rye-pasta (low insulin response) or an oat-wheat-potato (high insulin response) diet for 12 wk. In individuals in the low insulin response group, genes linked to insulin-signaling pathways and apoptosis. Gene expression of hormone-sensitive lipase was also downregulated. In contrast, individuals in the high insulin response group showed increased expression of 62 genes including of inflammation, interleukin cytokines, oxidative stress and heat-shock proteins while decreased expression was not seen for any gene. However, this study needs cautious interpretation because microarray analyses have well known technical limitations and statistical problems, especially when involving small sample size.

In summary, whole grain intake is associated with lower prevalence of the metabolic syndrome, BMI values, total cholesterol, and LDL-C levels and improves insulin sensitivity.

### Dietary micronutrients and insulin resistance

1. *Dietary magnesium*: Magnesium has been postulated to play a role in glucose homeostasis and insulin action<sup>136</sup>. An inverse association between magnesium intake and risk of T2DM has been found in most<sup>110,111</sup> but not in all studies<sup>137</sup>.

He *et al*<sup>138</sup> showed an inverse correlation between magnesium intake and fasting insulin levels among 4662 participants who were free from the metabolic syndrome and T2DM at baseline. They also showed that young adults with higher magnesium intake had lower risk of development of the metabolic syndrome. In addition, epidemiological studies and clinical trials indicate that magnesium intake may improve insulin sensitivity<sup>139</sup>. A few observational studies have investigated the association between magnesium intake and fasting insulin concentration exclusively in individuals without diabetes<sup>140</sup>.

Intracellular magnesium is a critical cofactor for several enzymes in carbohydrate metabolism,

and because of its role as part of the activated Mg-ATP complex required for all rate-limiting enzymes of glycolysis, regulates the activity of all enzymes involved in phosphorylation reactions. Magnesium concentration is critical in the phosphorylation of tyrosine kinase of the insulin receptor as well as all other protein-kinases, all ATP and phosphate transfer-associated enzymes, such as the Ca-ATPase in plasma membrane and endoplasmic reticulum. Hence, magnesium deficiency may result in altered tyrosine kinase activity on insulin receptor, an event related to the development of post-receptor insulin resistance and decreased cellular glucose utilization<sup>136</sup>.

**2. Dietary calcium:** Calcium and vitamin D, two major components of dairy products, have been postulated to be primarily responsible for the beneficial effect of dairy consumption on body weight and insulin sensitivity<sup>141,142</sup>. Liu *et al*<sup>143</sup>, in a large cohort of 10,066 women aged  $\geq 45$  yr, observed a significantly lower prevalence of the metabolic syndrome among those with higher calcium intake. Sun *et al*<sup>144</sup> showed significant positive correlations between total serum calcium concentrations with fasting serum glucose, insulin resistance and significant inverse correlation with  $\beta$ -cell function in women but not in men.

However, the underlying cellular or molecular mechanism by which calcium intake influences insulin resistance is unclear. Recently, animal and human studies indicated that high calcium intake might decrease levels of parathyroid hormone and 1,25 hydroxy (OH) vitamin D and thus influence adipocytes metabolism by inhibiting lipogenesis and stimulating lipolysis<sup>145</sup>.

**South Asian diets, insulin resistance and metabolic syndrome:** Asian Indians have a high prevalence of metabolic syndrome that may underlie their higher tendency to develop T2DM and early-onset cardiovascular disease. Certain features of the metabolic syndrome that have been reported among migrant South Asians and Asian Indians include dyslipidaemia, comprising a raised plasma triacylglycerol concentrations, reduced HDL-C concentrations and increased circulating levels of the atherogenic small-dense LDL particles<sup>146</sup>. Additional metabolic abnormalities typically observed in Asian Indians as compared to white Caucasians include high percentage of body fat, central obesity, insulin resistance, high procoagulant tendency, and increased prevalence of sub-clinical inflammation as denoted by high CRP levels<sup>147</sup>. Further, high prevalence of

obesity, dyslipidaemia and insulin resistance has been shown in urban Asian Indian children and adolescents<sup>146,148</sup>. Genetic predisposition, rapidly changing lifestyle, physical inactivity and migration have been postulated for greater occurrence of the above abnormalities; however, dietary profile has been less investigated<sup>147,149</sup>.

South Asian have higher proportion of total fatty acids as the  $\omega$ -6 PUFAs and a lower proportion of the LC  $\omega$ -3 PUFAs in plasma and membrane phospholipids compared with matched white Caucasians<sup>17,150</sup>. This could be due to higher intake of  $\omega$ -6 PUFAs, lower intake of  $\omega$ -3 PUFAs and higher  $\omega$ -6/ $\omega$ -3 PUFAs ratio as compared with white Caucasians<sup>17,150-152</sup>. Further, this could be due to low activities of  $\delta$ -5- and  $\delta$ -6-desaturases, which are necessary for the formation of LC  $\omega$ -3 PUFAs and/or the presence of certain dietary factors that interfere with the formation of EPA and DHA or their actions, such as high intake SFAs or TFAs, or the absence or deficiency of cofactors that are essential for the normal activity of desaturase, such as vitamin C, selenium, folic acid, vitamin E, pyridoxine, and  $\beta$ -carotene<sup>153</sup>.

Unfortunately, the data regarding dietary nutrients and their relation with insulin resistance are scarce in Asian Indians. Lovegrove *et al*<sup>17</sup> studied the impact of fish oil supplementation in 44 Europeans and 40 Indo-Asian Sikhs. They showed that LC  $\omega$ -3 PUFAs supplementation significantly decreased concentrations of plasma triacylglycerols, apo B-48, platelet phospholipids arachidonic acid and significantly increased HDL-C, platelet phospholipids EPA and DHA<sup>17</sup>. However, no effect of LC  $\omega$ -3 PUFAs supplementation on insulin sensitivity was reported<sup>17</sup>. Further, no significant effect of ethnicity on the response of fish oil supplementation was observed<sup>17</sup>. A study by Brady *et al*<sup>18</sup> reported the effect of fish-oil supplementation in a background of high or moderate  $\omega$ -6 PUFAs diet on fasting and postprandial blood lipids and on insulin resistance in 29 Asian Indians. They showed that high dietary intake of  $\omega$ -6 PUFAs did not attenuate the beneficial effects of fish-oil supplementation on the plasma triacylglycerol response. Further, LC  $\omega$ -3 PUFAs supplementation, whether given in combination with high or moderate  $\omega$ -6 PUFAs background dietary intake, had no effect on insulin sensitivity.

Asian Indians in India consume relatively more carbohydrates (~60-67% of the energy intake)<sup>154,155</sup>

as compared to the migrant Asian Indians in UK (~46% of the energy intake)<sup>211</sup> and USA (~56-58% of the energy intake)<sup>157,158</sup>. Sevak *et al*<sup>159</sup> assessed postprandial insulin concentrations in response to glucose load in 173 South Asians and European men and had the advantage of using 7-day weighed intakes. These investigators found that carbohydrate intake (as a percentage of total energy) was inversely correlated with insulin sensitivity (*i.e.*, total carbohydrate and sucrose were positively correlated with insulin resistance), with a stronger correlation for sucrose than for starch. The same pattern was seen for fasting insulin, but the correlation was weaker. Further, high carbohydrate intake was reported to induce hypertriglyceridaemia<sup>160,161</sup>. Another consistently recorded observation in Asian Indians has been low intake of dietary fiber<sup>162</sup> but its metabolic and clinical correlates have not been investigated in this ethnic group.

Diet and insulin resistance has been rarely investigated in children and adolescents, and a few investigations have been done in Asian Indians. In another dietary intervention study, it has been shown that obese adolescents failed to increase insulin sensitivity but rather increased insulin secretion to maintain normoglycaemia on high-carbohydrate/low-fat diet<sup>163</sup>. However, the number of subjects was less and the dietary interventions were of short duration. Kaitosaari *et al*<sup>164</sup> investigated the effect of dietary saturated fat intake on insulin sensitivity in 1062 healthy 7 month-old Finnish infants. Each year, two individualized counselling sessions were organized to each intervention family and they presented data of 167 children at 9-yr age. They showed that insulin resistance was lower in intervention children and there was a significant association between saturated fat intake and insulin resistance.

Studies have shown that low birth weight of Indian babies predict insulin resistance and adiposity in childhood<sup>165</sup>. Recently, Yajnik *et al*<sup>166</sup> reported that maternal macronutrients intake is unrelated to adiposity and insulin resistance in Indian offspring. However, higher maternal folate concentrations predicted greater adiposity and higher insulin resistance and lower vitamin B<sub>12</sub> predicted higher insulin resistance. In a cross-sectional study, we have recently investigated dietary nutrients influence on insulin resistance in 352 healthy Asian Indian adolescents and young adults, and showed that the intake of PUFAs was high, SFAs and  $\omega$ -6/ $\omega$ -3 PUFAs ratio was in upper limit and  $\omega$ -3 PUFAs (%en) was lower than recommended dietary allowance

(RDA) for Asian Indians. Further,  $\omega$ -6 PUFAs intake and BMI were significant independent predictors of fasting hyperinsulinaemia. More importantly, those subjects with lower than recommended intake of  $\omega$ -6 PUFAs exhibited less fasting hyperinsulinaemia. Specifically, the mean fasting serum insulin levels were lower when dietary  $\omega$ -3 PUFAs was as per recommended allowance while  $\omega$ -6 PUFAs was <7 per cent of caloric intake<sup>167</sup>. In addition, we have shown that SFAs is an independent correlate of high CRP levels in Asian Indian adolescents and young adults<sup>168</sup>. Based on our observations, if saturated fat intake is decreased to <7 per cent of caloric intake, then the mean CRP levels in the Asian Indian should decrease to <1 mg/l, placing them in low-risk category of CVD. In view of increasing obesity and high prevalence of cardiovascular risk factors in urban adolescents and young adult population in India, it is prudent to restrict the intake of  $\omega$ -6 PUFAs and SFAs, and to increase intake of  $\omega$ -3 PUFAs. Detailed dietary studies and intervention trials are required to evaluate the effects of dietary nutrients on insulin resistance.

### Summary

Data suggest that dietary  $\omega$ -3 PUFAs increase EPA and DHA content of phospholipids membrane, improve lipid profile and may have beneficial effect on insulin resistance. Dietary SFAs intake is positively associated with insulin resistance. Replacing dietary SFAs with PUFAs or MUFAs can have positive effects on insulin sensitivity. Recent data suggest that either of CLA bioactive isomer c9t11 and t10c12, increase insulin resistance and mixture of both isomers do not increase insulin resistance. High sucrose/fructose diet increase body weight, and risk for T2DM, and may have deleterious effect on insulin sensitivity. Evidence suggests that high carbohydrate diets increase concentrations of plasma triglycerides and decrease HDL-C and LDL-C and cause postprandial hyperinsulinaemia. However, it is still not clear from the available data whether the clinical utility of increasing the fiber content or decreasing the GI of low-fat/high-carbohydrates diets is preferable to simply replacing saturated fat with unsaturated fat and decreasing carbohydrates intake to decrease insulin resistance.

Genetic predisposition, dietary habits, rapidly changing lifestyle, physical inactivity and migration are contributory factors for high prevalence of insulin resistance in Asian Indians compared with white

Caucasian and in-depth investigations on these issues are required. Asian Indians and South Asians have higher intakes of carbohydrate and  $\omega$ -6 PUFAs, lower intakes of  $\omega$ -3 PUFAs and fiber, and higher  $\omega$ -6/ $\omega$ -3 PUFAs ratio as compared to white Caucasians. Recently, our group has reported that dietary  $\omega$ -6 PUFAs intake is significant independent predictors of fasting hyperinsulinaemia in young Asian Indians.

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