NFI BULLETIN
Bulletin of the Nutrition Foundation of India
Volume 28 Number 1 January 2007

Role of Muscle in Fat/Glucose Metabolism and Insulin Resistance

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Insulin resistance (IR) and obesity, which are part of the metabolic syndrome, are among the important antecedents to the development of non communicable diseases of aging (NCD) such as diabetes and coronary heart disease (CHD), which are increasing rapidly in India[1,2]. At a metabolic level, IR translates into an inefficient insulin function in end organs such as skeletal muscle, liver and adipocytes. IR is strongly associated with measures of overall obesity and the location of body fat in Indians[2,3]. The greater predilection for Indians to develop IR at low body weight may, in part, be due to their relatively greater adiposity at a lower body mass index (BMI) compared with other ethnic groups, both within and outside Asia[3-7]. However, while total body fat, or its distribution are important determinants of IR, it is important to independently assess the role of skeletal muscle. There are several considerations in this assessment, which include the actual muscle mass, fiber type, the accumulation of fat within muscle, and muscle metabolism in response to dietary stimuli and physical activity.

BMI, Muscle Mass and Fiber Type

A simple framework for the assessment of the effect of skeletal muscle on IR would be one which considered the effect of total body muscle mass, which has an independent effect on insulin sensitivity and glucose disposal[8-11]. It may be that Indians have a lower total body muscle mass, since a large percentage of Indians have a low to normal BMI[12], and studies on Indians or Asians (adult and pre-pubertal children) have indicated that they have a relatively low muscle mass as well, in comparison to Caucasian and African Americans[6,13,14]. It is not clear if the cause for this is genetic, or related to environmental factors. In Indians, a low muscle mass can be further worsened by chronic undernutrition[15]. Several studies in Indians within a BMI range of 23 to 25 kg/m^2 have shown lower insulin sensitivity in these subjects compared to age and BMI matched Caucasian counterparts[3,16,17]. While an inverse relation between glucose disposal rate or the insulin sensitivity index and visceral, subcutaneous and total fat has also been observed for both Indians and Caucasians[16,17], the curve for each of these age and BMI matched groups was different, with different intercepts. The latter point would suggest that factors other than the body fat and its location are operative in determining insulin sensitivity. Indeed, the insulin sensitivity index of Indians remained lower than that of age and BMI matched Caucasians even after adjustment for total body fat and truncal skinfold thickness[16]. Habitual physical activity levels and muscle mass are two factors that may explain the observed differences between Indians and Caucasians. Although muscle mass was not measured in the afore-mentioned studies, Raji et al[17] described their Indian subjects as being much less active than their Caucasian counterparts. The need for data on IR in subjects with similar muscle mass but different physical activity levels is evident.

However, a simple framework of a low total body muscle mass and a high risk of IR is insufficient when one considers the complexity of skeletal muscle fiber type, fat accumulation within muscle and the large number of intermediary regulatory molecules that operate within this tissue. The heterogeneity of muscle within the body is also relevant as glucose clearance is different across different muscle beds in the upper and lower limb of Type 2 diabetic patients[18]. Comparison studies between African American and Caucasian women have revealed that the former had lower insulin sensitivity in spite of having a higher muscle volume[19]. Indeed, the skeletal muscle volume accounted for the difference in insulin response between the groups. The reason for the higher muscle volume could conceivably be due to fat accumulation within the whole muscle. Intramyocellular lipid (IMCL) has been described earlier[20] and it has been speculated that the insulin resistance in Indians may be partly due to this alteration in muscle[2]. In addition, fat can be deposited between muscle fibers as intermuscular adipose tissue (IMAT)[21], and this has also been

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shown to be independently related to IR in African American women, even though it only weakly attenuates the significant difference in IR between African American and Caucasian women[19]. While this suggests that simple muscle bulk measurements may not suffice any longer, it must be pointed out that all the foregoing assessments were made in women with a BMI near 30 kg/M^2, and that in lower BMI Indians with a possible low insulin sensitivity, the total muscle mass may still have a negative association with IR. Furthermore, this also underscores the necessity for functional measurements to assess the role of muscle in IR and NCD. Muscle strength, which is known to decline with age[22], has been shown to predict all cause mortality independent of BMI in middle aged American Japanese men[23]. Cross-sectional studies on young South Indian men with chronic undernutrition have shown that they have a reduced forearm skeletal muscle mass and hand grip strength[24]. Fiber types in muscle are relevant and there is a significant reduction in the proportion of slow oxidative fibers and a significant increase in the proportion of fast glycolytic fibers in muscle from type 2 diabetic patients, contributing to the reduced oxidative capacity of skeletal muscles of type 2 diabetic patients[25]. This is relevant as described below.

Muscle and Insulin Resistance

Normal living is a state of alternating feeding and fasting. During the former, muscle stores are replenished, and during the latter stores are used up, and skeletal muscle adapts well to these fluctuations by increasing its reliance upon fat oxidation[26]. This flexibility of fuel selection allows for sparing muscle glycogen during exercise and reducing the uptake of plasma glucose. The decrease in muscle glucose uptake is accompanied by a reduction in oxidative glucose disposal with little change in non-oxidative glucose disposal[27,28]. The oxidative disposal of glucose is dependent on suppression of pyruvate dehydrogenase complex (PDC) activity, which in turn is inhibited by phosphorylation of its E1 component by pyruvate dehydrogenase kinase (PDK). In humans, 48 hours of starvation has been shown to downregulate the expression of hexokinase II activity five-fold whereas PDK expression was upregulated four-fold[29]. The important finding in this study was that starvation did not affect the expression of genes involved in fat metabolism, and that the change in substrate oxidation was dependent on downregulating the enzymes involved in oxidative glucose metabolism[29]. An interesting study on expression profiling of muscle mRNA after weight loss in morbidly obese women was able to map three important genes into the same network that was responsive to weight loss[30]. These were growth factor receptor-bound protein 14 (GRB14), glycerol-3-phosphate dehydrogenase 1 (GPD1), and growth differentiation factor 8 (GDF8; myostatin), which significantly reduced by about half or more, after weight loss[30]. While GRB14 inhibits the action of insulin and GPD1 is associated with increased triglyceride synthesis, GDF8 or mysotatin negatively regulates muscle mass[31]. Expression profiling may be a relatively blunt tool especially in studies of a small number of subjects; however, this study raises the interesting linkage of a gene for muscle mass with those related to insulin sensitivity.

Skeletal muscle, in a state of IR, has an increased muscle glucose oxidation under basal conditions[32]. This is in contrast to what might be expected due to the Randle effect[33], which hypothesizes that increased fat availability and oxidation in muscle would lead to a reduced glucose oxidation via the effects of acetyl-CoA on pyruvate dehydrogenase. In essence, therefore, IR could produce a state of "metabolic inflexibility", which would contribute to the accumulation of triglyceride within the myocyte[34]. This has also been confirmed in human muscle culture experiments where the capacity for fat oxidation by skeletal muscle was increased in subjects with increased insulin sensitivity, leanness, and aerobic fitness[35]. This is consistent with observations in whole body experimentation, where fasting skeletal muscle in individuals with type 2 diabetes and obesity showed (through measurements of the respiratory quotient across the lower limb tissue bed) increased levels of carbohydrate oxidation in type 2 diabetes and in obesity[36], and this low ratio of (fasting) fat to carbohydrate oxidation is thought to be predictive of weight gain[37]. A note of caution however is to be sounded about the universal applicability of these findings: while muscle triglyceride (as IMCL) was related to insulin sensitivity in Europeans, it was not similarly related in South Asians, suggesting that other factors may be important in this population[38].

Fatty Acids and Muscle Function

An increase in circulating free fatty acids (FFA) due to increased fat mass can precipitate a state of IR through a variety of mechanisms and there may be no single or common defect that can be pinpointed. Some of these are described below. Skeletal muscle glucose-6-phosphate levels decrease during glucose clamp studies when circulating FFA levels are elevated by lipid/heparin infusion[39], along with a lower intracellular free glucose levels indicating that FFA directly inhibit glucose transport and phsophorylation. Lipid infusions lead to a decrease in both insulin-stimulated tyrosine phosphorylation of insulin receptor substrate (IRS)-1 as well as activation of phosphoinositide-3 kinase 3 (PI3K) in skeletal muscle[40]. These are important downstream signaling mechanisms for glucose transporter translocation, although their role is still to be fully elucidated. Palmitic acid (C16:0) has been shown to be a potent inhibitor of insulin-induced glucose transport[41], through inhibition of the serine/threonine kinase Akt, also known as protein kinase B (PKB), which acts downstream of IRS-1-coupled PI3K. In mice skeletal muscle cells, palmitate is a potent inhibitor (by 50%) of the insulin receptor signal based phosphorylation of PKB/Akt, which in turn is responsible for translocation of glucose transporters (GLUT 4)[41]. Both LCFA-CoAs and DAG can activate protein kinase C (PKC), especially atypical PKC isozymes such as PKC θ[42]., which can serine phosphorylate IRS-1 and impair its ability to associate with the insulin receptor[43], thereby interfering with PI3K activation. Recent studies have also implicated c-jun amino-terminal kinase (JNK) as a mediator of FFA induced insulin resistance[44]. JNK is a member of the p42/p^{44} mitogen-activated protein (MAP) kinase superfamily which consists of downstream signaling molecules of the insulin pathway. JNK is activated by FFA[45] and influences gene transcription by transcription factors such as c-jun and ATF 2 (activating transcription factor 2), suggesting a role for this interaction in impaired insulin signaling[46]. Another mechanism by which elevated FFA levels may impair insulin signaling is by its conversion to long-chain

fatty acyl-CoAs (LCFA-CoA) whose muscle levels have been shown to be negatively correlated with whole body insulin sensitivity[47]. If not oxidized in the mitochondria, LCFA-CoAs are re-esterified via diacylglyercol (DAG) to form triglycerides and phospholipids. Increased intramyocellular triglyceride content is seen in obesity and type 2 diabetes[48] and is a strong predictor of insulin resistance in both animals and humans[49,50], probably as a marker of increased intracellular LCFA-CoAs and lipid intermediates. Mitochondrial function is also influenced by fat; the feeding of a high fat diet (50% fat) for 3 days to healthy volunteers resulted in the decreased expression of genes involved in oxidative phosphorylation in the mitochondria, as well as a decrease in the expression of PPAR γ coactivator1, consistent with mitochondrial dysfunction[51] similarly, reduced mitochondrial oxidative phosphorylation activity could be demonstrated in the lean offspring of type 2 diabetic parents[52]. These findings suggest that the genes for mitochondrial biogenesis, while susceptible to environmental stimuli such as dietary intake of fat, may also be the genetic basis for the inheritance of diabetes.

While FFA promote a state of IR, studies have shown PUFA (particularly of n-3 origin) to exert protective action and hence, the dietary intake of an appropriate ratio of n-3 and n-6 fatty acids is important. Polyunsaturated n-3 fatty acids can act as agonists of peroxisome proliferation activation receptor (PPAR) γ[53], similar to the therapeutic agents like the glitazones (which belong to the thiazolidinedione group). PPAR has several effects on gene expression[54], and can therefore, n-3 fatty acids can take part in several distinct but interacting pathways in muscle, and may increase GLUT 4 transcription[53]. Intake of polyunsaturated fatty acids (PUFA) of marine origin, namely eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3), have been shown to be hypolipidemic, exert prophylactic effects on cardiovascular disease, protect against insulin resistance and obesity in rodents fed high-fat diets, and reduce insulin response to glucose in healthy humans[55-57]. The effects of n-3 and n-6 ratios can also be seen through studies of whole body insulin sensitivity which correlated with the amount of long chain, unsaturated fatty acids (C20–C22) in membrane phospholipids of human thigh muscle[58] and it is reasonable to think that the fatty acid composition of muscle cell membranes reflects dietary fat intake, as demonstrated in animal studies[59]. The importance of these observations cannot be overstated. Studies of populations specifically prone to obesity and type 2 diabetes (such as Pima American Indians) show that they have much lower levels of n-3 fatty acids in their muscle membrane lipids than Caucasian counterparts[60]. More importantly, dietary interventions have been shown to increase n-3 fatty acids in skeletal muscle membrane phospholipids of obese subjects[61], and reducing the n-6:n-3 ratio of dietary fat (to at least 10) prevented sucrose induced insulin resistance in rats[62]. In India, the intake of n-3 fatty acids is particularly low, and DHA intakes are practically non-existent[63]. The consumption of vanaspati, a fat rich in trans-fatty acids is of concern, as this also leads to insulin resistance in rats[64].

Protein, Amino Acids and Muscle

The dietary intake of amino acids is also relevant, since essential amino acids produce a rapid increase in plasma amino acid concentrations and can stimulate skeletal muscle protein synthesis to a greater extent than nonessential amino acids[65]. Indeed, amino acids given alone can never be utilized efficiently, and the combined effect of essential amino acids along with carbohydrate is optimal. In the elderly, studies have shown that the daily supplementation of hydroxymethylbutyrate, arginine and lysine for 12 wk positively alters measurements of functionality, strength, fat-free mass, and protein synthesis[66]. The effect of lysine is of interest, particularly in view of the daily requirement of 30 mg/kg/day[67] or higher in chronic undernutrition[68], for this amino acid (which is more than double the requirement laid out in the 1985 WHO/FAO/UNU expert consultation[69]) and its limiting nature in cereal based diets. Lysine intakes are marginal in low socio-economic group Indians[67,68] and there are several lines of reasoning to suggest that lysine intake may influence muscle function and that protein accretion may be taking place in chronically undernourished individuals who are simply exposed to a more complete diet, without the benefit of additional exercise. First, well nourished Indians showed a trend toward improved muscle function with higher lysine intakes[70], as have elderly women[66]. Second, the lysine requirement of undernourished subjects placed on perfectly adequate diets for one week was 50% higher than that of well-nourished subjects[68]. Third, in similar undernourished subjects, the leucine balance (an indicator of whole body protein balance) at different lysine intakes after they were successfully treated for intestinal parasites was positive at high lysine intakes[71]. None of these subjects increased their physical activity during these experiments. Fourth, a recent study using compilations of data on weight, height, dietary energy and protein from different regions of China showed that lower protein intake was related to growth failure while energy was not[72]. While this study did not distinguish between animal and plant protein, nor was it able to assign a value to the effect of micronutrients that accompany protein, it broadly reached similar conclusions as other studies which assessed the effect of animal protein on growth[73]. If protein quality is assessed through the use of the protein digestibility adjusted amino acid score (PDCAAS), and assuming lysine to be the first limiting amino acid in cereal protein, then it becomes evident, with the new higher daily lysine requirement, that the protein quality of Indian diets is particularly poor with PDCAAS adjusted Protein:Energy (PE) ratios of about 0.08 for average Indian diets[74]. This would mean that between 15 to 45% (depending on age and gender) of the sedentary Indian population would be at risk for protein deficiency, since a sedentary activity pattern would automatically raise the required PE ratio of the dietary requirement. This in itself is good cause to recommend increased physical activity in Indians, as it would then drop the PE ratio of their required dietary intake. Leucine is also an amino acid of interest as it can act as a signal to increase muscle protein synthesis in addition to its role as a substrate. However, this increased protein synthesis (in infusion protocols) shows tachyphylaxis in 2 hours explaining why chronically elevated leucine delivery does not elevate muscle protein synthesis in clinical situations[75]. The stimulation of muscle protein synthesis by leucine is associated with an elevation of signaling activity in the mammalian target of rapamycin (mTOR)/p70 ribosomal subunit pathway[76]. It is however, im-

portant to separate out the effect of amino acid supplementation from other factors, like for example, physical activity, since the latter can completely obscure the amino acid effects.

Exercise and Muscle

Finally, the effect of exercise dominates the environmental effects on muscle, and there are several epidemiological studies that have shown a beneficial effect of exercise on diabetes[77-82]. Exercise and muscle contraction acutely activates glucose transport independent of insulin, and is associated with later effects on insulin sensitivity[83]. Aerobic exercise can improve insulin sensitivity[84] through defined biochemical mechanisms in muscle[85,86]. Resistance exercise has also been shown to improve whole-body insulin sensitivity in healthy males, through the acute reduction of imtramyocellular lipids, although the lipid content of muscle is regained during recovery from exercise[87]. It is possible that a lowered muscle mass may have a role in increasing fat accumulation as muscle fat oxidation, linked to daily physical activity, is an important determinant of whole body fat oxidation[88]. A study on the effects of endurance and resistance training in non obese young women showed that insulin sensitivity improved through intrinsic (with endurance training) and muscle mass based (with resistance training) mechanisms, even though there were no changes in total body, subcutaneous or visceral fat after 6 months of training[11]. Further evidence for the importance of physical activity and muscle mass comes from intervention studies, where a high physical activity has been shown to increase fat free mass (probably muscle) and reduce fat mass by small but significant amounts[89]. Lifestyle interventions including diet and physical activity have also been shown reduce the incidence of diabetes, even when weight did not change[90]. A similar decline in the age adjusted risk for CHD, hypertension and diabetes with increasing leisure time physical activity has also been demonstrated for middle aged men and women[91].

Conclusion

In India, it would seem that an unfortunate combination of all the foregoing factors that promote IR are in place with nutritional and lifestyle transitions resulting in high fat but low n-3 fatty acid intakes[63,92,] coupled with a low physical activity[93,94,] and a low quality protein intake[71,75]. Indeed, the low physical activity puts an added requirement on the diet of a higher PE ratio, which is difficult to meet with diets that already have low protein quality. It would seem important therefore, to focus efforts on improving muscle physiology and function in addition to reducing fat, in the prevention of NCD. These intertwining environmental effects would not only increase total body fat mass, but might also result in a relatively lower body muscle content with less functionality, ultimately resulting in insulin resistance and non-communicable chronic disease.

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FOUNDATION NEWS

● **The Annual Day of the Foundation** was celebrated on November 29, 2006.

C Ramachandran Memorial Lecture

Dr D Banerji, Professor Emeritus, Department of Social Medicine and Community Health, JNU delivered the C Ramachandran Memorial Lecture on "Primary Health Care in India: How to achieve what Bhore Committee envisaged?"

Symposium on "Primary Health Care – New Initiatives"

NFI in collaboration with Government of India and WHO organised a two-day symposium on "Primary Health Care – New Initiatives" at India International Centre, on November 30th and December 1st, 2006. The Symposium was inaugurated by Mr Cecilio Adorna (Country Representative, UNICEF).

● **National Academy of Medical Sciences (NAMS)**

In recognition of his outstanding contribution to Medical Sciences and Biochemical Research, Dr C Gopalan – President NFI, has been conferred Life Time Achievement Award of NAMS for the year 2006.

Dr Prema Ramachandran, Director NFI has been elected as the President of NAMS. She will hold the office for three years.

NUTRITION NEWS

● **Nutrition Society of India**

The XXXVIII Annual Conference of Nutrition Society of India was held in November 2006 at AIIH&PH, Kolkata. The theme of the meeting was "Nutrition in Different Stages". Dr. M.K. Bhan, delivered the thirtieth Gopalan Oration on "Preparing to face the Challenge". Eighteenth Srikantia Memorial Lecture was delivered by Dr. K. Vijayaraghavan, on "Community Nutrition Research in India – Contributions, Constraints and Controversies". During the Conference two symposia were also organised: "Infant Feeding and Growth" and "Nutrition and Development"

Mrs Anshu Sharma from NFI presented a paper on "Detection and Management of Anaemia in Pregnancy in an Urban Primary Health Care Institution" in this meeting and was awarded Young Scientists' Senior Award in Community Nutrition.

● **Kamla Puri Sabharwal Memorial Lecture**

Dr Sushma Palmer delivered the XXXIII Kamla Puri Sabharwal Memorial Lecture on November 16, 2006. The title of the lecture was "Global Health in Transition: The case for eating Green and Promoting Health".