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REVIEW ARTICLE

Physical inactivity and obesity: links with insulin resistance and type 2 diabetes mellitus

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Summary

Data from the health survey for England 2006 [1], showed that the prevalence of type 2 diabetes mellitus (T2DM) has more than doubled in men and women since 1991. In the USA certain States have a prevalence of T2DM of greater than 10% [2]. Globally it has been reported that this increase is by no means slowing down and that the number of individuals with the disease is expected to rise from 171 million cases reported in 2000 to 366 million by the year 2030 [3]. Physical inactivity and obesity are two major risk factors for the development of T2DM. In this review we will discuss evidence of an association between physical inactivity, obesity and T2DM from prospective cohort studies and clinical trials. We will also discuss some of the potential mechanisms that are thought to link obesity and physical inactivity with the major pathophysiological precursor of T2DM, insulin resistance. Copyright © 2009 John Wiley & Sons, Ltd.

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Prospective studies and clinical trials

Many prospective studies have been published over the last two decades reporting strong associations between daily physical activity and a reduced risk of developing T2DM (Table 1). Helmrich *et al*. investigated 5990 male alumni from the University of Pennsylvania and reported a negative relationship between incidence of type 2 diabetes and physical activity [4]. Indeed, for every increase in leisure time energy expenditure of 500 kcal, the age-adjusted risk for developing T2DM decreased by 6%. This relationship held strong even when adjustments were made for obesity, hypertension and a parental history of diabetes. These findings were later replicated in a much larger cohort of women. The Nurses' Health Study [5] followed 70 102 registered nurses and reported a progressive reduction in the age-adjusted relative risk of T2DM with increasing physical activity.

Following on from these earlier studies, similar findings have been reported in studies across the globe. Studies from the UK [6], Japan [7], Finland [8] and Germany [9] have reported a reduction in relative risk for the development of T2DM of between 15 and 60% with increased daily physical activity. In addition, Hu *et al*. [8] displayed eloquently the relative risk of developing T2DM with not only physical activity quintiles but also those of body mass index (BMI) and impaired glucose regulation. The authors showed that an increase in BMI drastically increased the relative risk for development of T2DM whilst physical inactivity in normal weight individuals had a

Table 1. Prospective studies implicating physical inactivity as a risk factor in the development of type 2 diabetes

Author	Participants	Comments	Country of study
Helmrich *et al*. [4]	5990 M	↓ Age-adjusted risk of 6% every 500 kcal of leisure time physical activity	US
Perry *et al*. [6]	7735 M	↓ Relative risk of 60% between moderately active men and inactive men	UK[a]
Hu *et al*. [5]	70 102 W	↓ Relative risk of 26% between upper and lower quintile of physical activity	US[b]
Nakanishi *et al*. [7]	2924 M	↓ Adjusted relative risk of 59% between upper and lower quintile of physical activity	Japan
Hu *et al*. [8]	2017 M and 2352 W	↓ Adjusted relative risk of 15 and 57% between moderate and high compared to low physical activity	Finland
Meisinger *et al*. [9]	4069 M and 4034 W	↓ Adjusted relative risk of 13, 30 and 76% between low, moderate and high compared to no physical activity	Germany[c]

M, men; W, women.
[a]British Regional Heart Study.
[b]The Nurses' Health Study.
[c]The MONICA/KORA Augsburg Cohort Study.

much attenuated effect. Pooling the data they concluded that those individuals with a BMI $\geq$30 kg/m^2, partake in low levels of physical activity, have impaired glucose regulation and are 30 times more likely to develop type 2 diabetes than normal weight, active normal glucose tolerant individuals. A similar finding was reported by Weinstein *et al*. [10] who followed 37 878 women for an average of 6.9 years. They concluded that both BMI and physical inactivity were predictors of T2DM incidence, but that the magnitude of the association with BMI was greater than with physical inactivity.

In addition to the aforementioned prospective studies, clinical trials, in which lifestyle modifications were made, have reported that the addition of physical activity and dietary modification can reduce the incidence of T2DM. The Da Qing Impaired Glucose Tolerance (IGT) and Diabetes Study [11] investigated 577 men and women with IGT every 2 years over a 6-year period. The men and women were randomized into one of four groups; control, diet only, exercise only and diet plus exercise. The cumulative incidences of T2DM after 6 years were 67.7% for control, 43.8% for diet only, 41.1% for exercise only and 46.0% for diet and exercise. When adjusted for difference in baseline BMI and fasting glucose the risk of developing T2DM was decreased by 31% by diet only, 46% by exercise only and 42% by diet and exercise.

Furthermore, The Diabetes Prevention Program [12] a large randomized clinical trial in adults at risk for the development of T2DM, compared lifestyle intervention with drug therapy. A total of 3234 participants were assigned to one of three groups; control, metformin and lifestyle intervention for an average of 2.8 years. The lifestyle intervention was designed such that individuals achieved and maintained weight loss of 7% and engaged in physical activity for 150 min/week. Participants in the lifestyle modification group lost significantly more weight and increased physical activity to a greater extent than either the metformin or control groups. Both the metformin and lifestyle modification groups had a significant reduction in the cumulative incidence of T2DM compared to the control group (58% and 31%, lifestyle and metformin respectively). Interestingly, the lifestyle intervention was far more effective in reducing the risk of developing T2DM than the metformin group.

In summary, it has been shown that obesity and physical inactivity are risk factors for the development of T2DM. Furthermore, 80% of type 2 diabetics are obese and sedentary. It appears that a sedentary lifestyle (physical inactivity) results in various symptoms of disease reduced insulin sensitivity in the early stages and T2DM as the disease is progressing. It is therefore important to understand how inactivity causes IGT, reduced insulin resistance and ultimately T2DM. In healthy humans, skeletal muscle accounts for between 70 and 80% of insulin-stimulated glucose uptake [13] and, skeletal muscle is the principal peripheral site of insulin resistance in T2DM [14,15]. The muscle is also responsible for the most variable component of daily energy expenditure: the thermic effect of exercise. This component can be reduced to very low levels with a sedentary lifestyle. The remainder of this review will therefore focus on the underlying mechanisms within skeletal muscle thought to link obesity and a sedentary lifestyle with insulin resistance and the onset of T2DM.

Obesity, fatty acid uptake and oxidation

Where adipose tissue is the principal organ for fatty acid storage, skeletal and cardiac muscle are the most important organs for fatty acid oxidation. Fatty acids are mobilized from adipose tissue and transported to the muscle for uptake and oxidation. In obesity, there appears to be a mismatch between uptake of fatty acids into skeletal muscle and oxidation, leading to excessive accumulation of triacylglycerol and fatty acid metabolites such as long chain acyl-CoAs, diacylglycerols and ceramides in the sarcoplasm.

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Increased lipid accumulation within skeletal muscle may occur through two mechanisms; either an increased uptake and/or a decreased oxidation of fatty acids. In obesity skeletal muscle is usually chronically exposed to high plasma fatty acid concentrations which could drive an increased uptake into the muscle. However, it has been shown that the uptake of fatty acids (palmitate) into giant vesicles prepared from skeletal muscle is increased in insulin resistant skeletal muscle of obese Zucker rats [16] as well as obese and type 2 diabetic patients [17]. This increased uptake was observed even when the palmitate concentration in the bathing medium was equal and is suggested to be due to an increase in proteins involved in fatty acid uptake. Both fatty acid binding protein (FABPpm) [18] and fatty acid translocase (FAT)/CD36 [17] are increased in obesity. In the case of FAT/CD36 total protein content is not increased but it is permanently translocated from intracellular depots to the plasma membrane, thus facilitating fatty acid uptake [19]. Additionally, a second likely explanation for the accumulation of lipid within skeletal muscle is a reduction in fat oxidation. Dobbins *et al*. [20] reported that chronic inhibition (4-week) of fatty acid uptake into the mitochondria using a pharmacological inhibitor of carnitine palmitoyltransferase-1 resulted in intramuscular triacylglycerol (IMTG) accumulation and insulin resistance in rats. In humans a reduction in postabsorptive fat oxidation has been reported frequently in obesity and T2DM when compared with lean individuals [21–25] and this reduction remains post weight loss [26,27].

IMTG accumulation and insulin resistance

It has been suggested that the increased availability and uptake of circulating fatty acids alongside an impairment in the ability to oxidize fat lead to the accumulation of IMTG [20] and fatty acid metabolites such as long chain acyl-CoAs, diacylglycerols and ceramides in obesity. Elevated IMTG accumulation has been observed in obesity [28,29] and there is a large body of evidence to suggest that the accumulation of IMTG correlates with insulin resistance and the development of T2DM [28,30–37]. In addition to these observational studies, intervention studies that are typically associated with increased insulin sensitivity such as weight loss [38] have shown reductions in IMTG content [28]. Furthermore, increasing IMTG via high fat feeding can decrease insulin sensitivity in rats [39]. However, paradoxically, when endurance trained athletes are included in these relationships the strong correlation observed disappears [30,40] because endurance trained athletes are highly insulin sensitive yet have elevated IMTG content [30]. Further dissociation between IMTG and insulin resistance becomes apparent when examining recent exercise training data. Exercise training can increase insulin sensitivity despite an elevated IMTG content in sedentary older adults [41] and sedentary overweight obese individuals [42]. As there is an apparent dissociation between IMTG content and insulin resistance it has been suggested that IMTG accumulation is a surrogate marker for the accumulation of other lipid intermediates that can modulate insulin signaling.

Fatty acid intermediates and insulin signaling

Studies in which circulating plasma fatty acid concentrations have been acutely raised have lead to insulin resistance in human skeletal muscle [19,43–45]. In addition chronic (4 d) lipid infusions have produced a similar response [46]. Conversely, pharmacological reduction in circulating plasma fatty acid concentrations using acipimox in individuals with chronically elevated fatty acid concentrations has been shown to improve insulin resistance overnight [47,48]. Furthermore, inactivation of fatty acid transport protein 1, which is important in fatty acid uptake and subsequent conversion to fatty acyl-CoA within the skeletal muscle prevents the insulin resistance observed with high fat feeding and lipid infusions in mice [49].

Belfort *et al*. [43] reported that an elevation in circulating fatty acids within the physiological range was associated with a decrease in insulin-stimulated insulin receptor tyrosine phosphorylation, insulin receptor substrate (IRS)-1 tyrosine phosphorylation, IRS-1 associated phosphatidylinositol (PI) 3-kinase activity, Akt serine phosphorylation and glucose disposal rates. In addition to the decreased insulin activation of IRS-1 tyrosine phosphorylation and IRS-1 associated PI3-kinase activity lipid infusion is associated with an increase in long-chain acyl-CoA and diacylglycerol content within the skeletal muscle [50,51].

There is now an attractive hypothesis that suggests a mechanistic link between the accumulation of fatty acyl-CoAs and diacylglycerols and insulin resistance (Figure 1). Skeletal muscle diacylglycerol content is increased in human and animal models of insulin resistance [50,51] and this can activate specific isoforms of protein kinase C (PKC) which can inhibit insulin signal transduction thought to be through serine phosphorylation of IRS-1 [51]. Aguirre *et al*. [52] have shown that phosphorylation on a specific serine site, serine 307, of IRS-1 can block the phospho tyrosine binding domain functions of the IRS-1 protein thereby inhibiting the downstream signaling events such as PI3-kinase activation.

Evidence implicating PKC comes from observations in lipid induced insulin resistance models. Griffin *et al*. [53], infused rats with lipid/heparin for 5 h and found that the membrane fraction of PKC θ was increased fourfold. This increase in membrane bound PKC θ was associated with a blunting in insulin-stimulated IRS-1 tyrosine phosphorylation and a 50% reduction in insulin-stimulated IRS-1-associated PI3-kinase activity. The same

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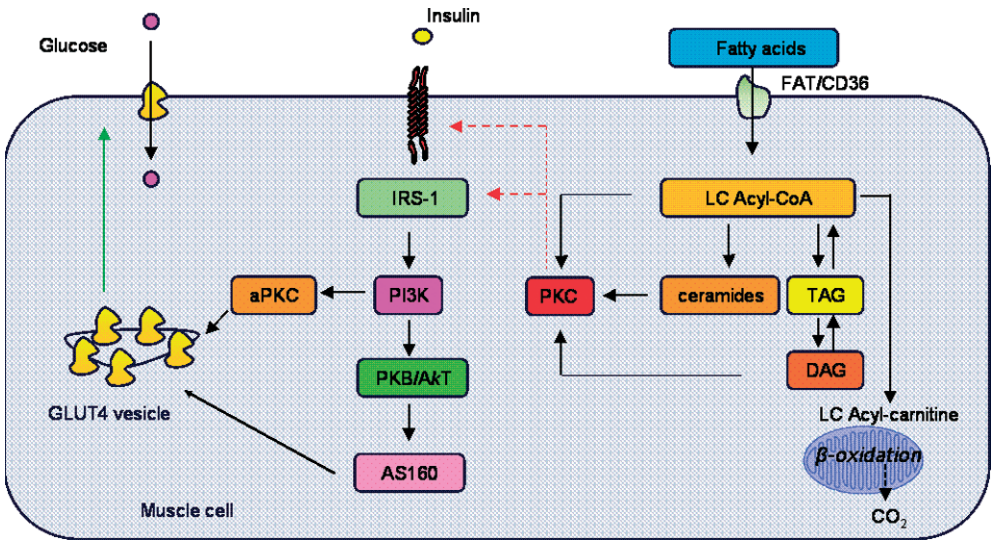

Figure 1. Lipids and insulin resistance. aPKC, atypical protein kinase C; IRS-1, insulin receptor substrate-1; PI3K, phosphatidyl-3-kinase; PKB, protein kinase B; AS160, Akt substrate of 160 kDa; nPKC, novel isoforms of PKC; LC, long chain; TAG, triacylglycerol; DAG, diacylglycerol; FAT/CD36, fatty acid translocase CD36. Dotted lines indicate inhibitory pathways, solid lines indicate activation

is evident in human models. When healthy volunteers were infused for 6 h with lipid/heparin a reduction in glucose disposal was associated with a four-fold increase in membrane bound PKC [50]. Moreover PKC θ knockout mice are protected against fat induced insulin resistance [54] and it has been demonstrated in cell lines [55–58] and rats [53,59,60] that PKC can inhibit IRS-1 tyrosine kinase activity and reduce insulin-stimulated glucose uptake. In human skeletal muscle strips a cause and effect relationship has been observed between PKC activation and insulin-stimulated glucose uptake. Using human skeletal muscle strips from lean and obese individuals Cortright *et al*. demonstrated that in insulin resistant muscle the addition of a PKC inhibitor could increase glucose uptake. Conversely in insulin sensitive muscle the addition of a PKC activator could depress insulin-stimulated glucose uptake [61].

β-Oxidation and insulin signaling

In contrast to the lipid accumulation theory, Perdomo *et al*. [62] demonstrated, in L6 myotubes, that an increase in β oxidation induced by an overexpression of carnitine palmitoyltransferase-1 increased insulin-stimulated glucose uptake in the absence of any perturbations in IMTG, diacylglycerol, ceramide or long chain acyl-CoAs. In line with this finding, recent data from Thyfault *et al*. [63] has indicated that elevations in mitochondrial oxidative capacity following an acute bout of exercise can increase insulin-stimulated glucose uptake in the absence of any decrease in diacylglycerol or long chain acyl-CoAs. Indeed, it was observed that long chain acyl-CoAs increased following exercise. It has therefore been speculated that acute exercise induces a coordinated increase in β-oxidation with an up-regulation of the tricarboxylic acid (TCA) cycle, such that complete fatty acid oxidation takes place [64] and the resultant acetyl-carnitines are immediately taken into the TCA cycle [63]

Conclusions

Being overweight or obese and leading a sedentary lifestyle are two significant predictors of insulin resistance and T2DM development. It would seem that the influence of overweight/obesity is far greater than that of being physically inactive when interpreting the magnitude of relative risk of T2DM development. Lifestyle interventions that include regular physical activity and dietary modification can delay and even prevent the onset of such diseases. A possible mechanism through which lifestyle interventions exert their effects is thought to include an increase in fat oxidation following a period of exercise training. This mechanism has been shown to reduce the accumulation of fatty acid species such as fatty acyl-CoAs, diacylglycerols and ceramides within the skeletal muscle, thus attenuating the inhibition on the insulin signaling pathway. Moreover, an early response to exercise training could include a coordination of the increase in β-oxidation with an up-regulation of the TCA cycle leading to a decrease in the accumulation of diabetogenic β-oxidation intermediates.

Conflict of interest

None declared.

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