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How much variance in insulin resistance is explained by obesity?

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Background: Obesity is believed to be the major cause of insulin resistance, although many other obesity-independent signals are shown to affect insulin sensitivity.

Aim: We address the degree to which variation in insulin resistance is explained by morphometric and biochemical measures of obesity.

Methods: PubMed and Google Scholar were searched for epidemiological studies published between 1994 and 2015 that report correlations between at least one measure of obesity and that of insulin resistance.

Results: A total of 63 studies satisfied inclusion criteria. Frequency distribution of coefficients of determination between morphometric measures of obesity and insulin resistance was skewed with the mode being less than 10%, class and median being 17.3%. Plasma leptin concentration, but not plasma non-esterified fatty acid level, was better correlated with insulin resistance, the median variance explained being 33.29%. Morphometric measures alone had a median variance explained of 16%. Ethnicity explained part of the variance across studies with the correlation being significantly poorer in Asians.

Conclusion: The extremely limited predictive power of morphometric and biochemical measures of obesity suggests that more research needs to focus on the obesity-independent signals that affect insulin sensitivity as well as leptin expression.

Introduction

Obesity is currently believed to be the major cause of type 2 diabetes mellitus (T2DM) characterised by insulin resistance. Among the currently perceived risk factors for T2DM, overweight and obesity are strongest.[1] Adipose tissue, implicated as a major determinant of insulin sensitivity and glucose homeostasis,[2,3] is no more considered an energy storage tissue alone and signals from this tissue affect many endocrine and metabolic functions of the body.[4,5] Various measures of obesity are generally significantly positively correlated with markers of insulin resistance. Although the correlation has different possible causal interpretations, such as hyperinsulinemia being causal to obesity, the mainstream view considers obesity to be the primary cause of insulin resistance. However, the relationship may not be as robust as classically believed.

Obese and metabolically normal individuals exist[6,7] and their proportion varies substantially between studies ranging from 6% to 75% of the obese population.[8,9] On the other hand, normal-weight, insulin-resistant individuals are also frequent.[10] Across countries, there is no correlation between prevalence of obesity and T2DM.[11] Indeed, as a prime example, Asians develop T2DM at much lower obesity levels.

Apart from adipocyte-derived signals, a number of other signals have been shown to affect insulin sensitivity partly or completely independent of obesity. They include autonomic and other neuronal signals,[12] epidermal growth factor, brain-derived neurotrophic factor (BDNF), fibroblast growth factor (FGF) and other growth factor signals.[13,14,15,16,17,18] Myokines, proteins from muscle tissue, have also been shown to affect insulin sensitivity.[19,20,21] Damage or soring of muscle reduces insulin sensitivity, an effect that is not restricted to the damaged muscle.[22,23,24,25] Infections[26,27] and pain[28] also affect insulin sensitivity. Thus, it is clear that apart from adiposity-related signals, a number of other mechanisms affect insulin signalling and glucose homeostasis. However, the relative role of obesity-related and obesity-independent signals in influencing the prevalence of insulin resistance in a population remains poorly understood.

We address a part of this broader question by asking how much of the variance in measures of insulin resistance (i.e. fasting plasma insulin, homeostatic model assessment – insulin resistance/

insulin sensitivity (HOMA – IR/IS), hyperinsulinaemic clamp and frequently sampled intravenous glucose tolerance test) is explained by obesity indices, namely body mass index (BMI), waist–hip ratio (WHR), waist circumference (WC), total fat (TF), plasma non-esterified fatty acids (NEFA) and plasma leptin, in epidemiological studies published between 1994 and 2015. The systematic review was registered with the International Prospective Register of Systematic Reviews (registration number CRD42016047499). The review design followed Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[29]

Research design and methods

Study design

We conducted a literature search using PubMed (Medline) and Google Scholar for studies examining correlation between obesity and insulin resistance or risk of type 2 diabetes published between 1994 and 2015. The key words used in combination for the search included: Type 2 diabetes mellitus (T2DM), Homeostatic model assessment – insulin resistance/ insulin sensitivity (HOMA – IR/IS), Frequently sampled intravenous glucose tolerance test (FSIVGTT), hyperinsulinaemic clamp, obesity, waist circumference (WC), non-esterified fatty acid (NEFA), leptin, waist-hip ratio (WHR), body mass index (BMI) and total fat (TF). The key word combinations used for search included (1) obesity or one of the specific measures of obesity, (2) insulin resistance or one of the specific measures of insulin resistance and (3) the word 'correlation'. We did not include pro-inflammatory cytokines in the study. Although adipocytes are known to secrete cytokines, they are not specific to adipose tissue. Because many different types of cells secrete pro-inflammatory cytokines, it would be difficult to draw clear-cut inferences from their correlations. Adiponectin is more specific to adipose tissue; however, its plasma level is not directly proportional to obesity. Therefore, we did not consider adiponectin as a surrogate of obesity.

Setting

The number of patients per study ranged from 21 to 4800. The studies covered different age groups, the net range being from 2 to 95 years.

Study population and sampling strategy

Papers reporting Pearson's correlation, Spearman's correlation or multiple regression including one or more measures of obesity and one or more measures of insulin resistance were included in the meta-analysis. Studies that divided the population in groups such as tertiles or quartiles and used group comparison statistics were excluded because different studies make different number of groups making comparisons across studies difficult. Two researchers screened all papers identified in the initial search, based on the inclusion criteria. In addition, the corresponding authors of 35 studies that did not report any correlations between measures of obesity and insulin resistance but had measured these parameters in a population were contacted to request access to raw data from which we could have calculated the required statistics. Four data sets coming from two research groups could be accessed, from which we could obtain 16 relevant correlations.

Data analysis

Many publications reported more than one correlation based on different measures of obesity and insulin resistance or based on distinct patient groups separated by gender, treatment, ethnicity, etc. As one approach to analysis, every correlation between a measure of obesity and that of insulin resistance was treated as an independent data point. In an alternative approach, to avoid pseudo-replication, we also analysed the data taking only the best correlation from each study. The coefficient of determination (R^2) or variance explained was extracted either as reported by the authors, or we calculated it from the reported data.

Results

Sixty-three studies were identified using the inclusion and exclusion criteria (see Appendix 1 for the complete list), which gave us 164 correlations between obesity measures and insulin resistance measures. In 10 studies, variance explained was reported, and R^2 could be calculated from published data from 48 studies and from raw data in 4 data sets.

The 164 R^2 values between measures of obesity parameters and those of insulin resistance ranged widely from 0 to 0.9 (non-significant ones being treated as zero). Frequency distribution (Figure 1) revealed that the mode was in the range of 0% – 10%, suggesting that in the majority of studies obesity explained only up to 10% variance in insulin resistance. The median variance explained was 17.3%. Taking 164 correlations from 63 studies involves some amount of pseudo-replication. To test whether the overall low mode

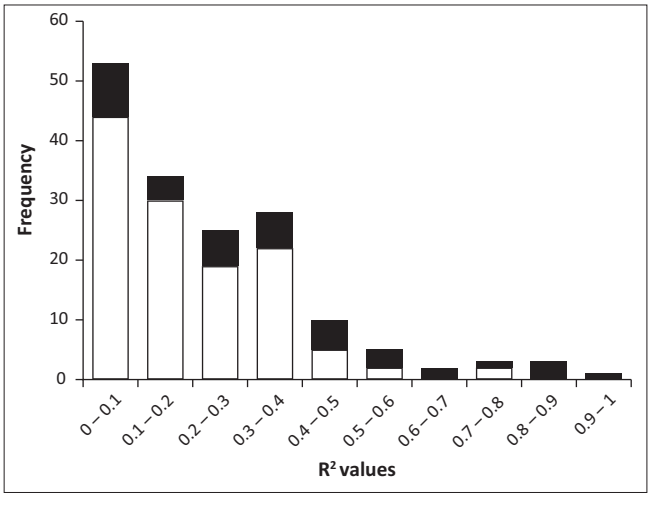

FIGURE 1: Frequency distribution of R^2 values. For all non-significant correlations, R^2 was treated as zero. Filled bars indicate correlations with plasma leptin concentrations. Open bars indicate all other correlations.

and median are artefacts of the pseudo-replication, we selected the largest R^2 value from each of the 54 studies. The median of this collection was higher (27.04%). A rise in the median was expected because the best correlation from every study was taken. It is important to note that despite taking the best, the median variance explained remains small.

Among various obesity-related parameters, leptin had better R^2 values than the other measures, the difference being significant by the median test (leptin correlations: 30 above the median and 10 below the median, chi-square = 10, $p < 0.0001$). NEFA correlations were significantly worse (1 above the median and 13 below, chi square = 10.28, $p = 0.001$). WHR (9 below the median 6 above, chi square = 0.6, $p = 0.438$), BMI (22 above the median 23 below, chi square = 0.8, $p = 0.881$), WC (14 below the median 10 above, chi square = 2.02, $p = 0.414$) and TF (14 above the median 12 below, chi square = 0.153, $p = 0.694$) did not differ significantly from the global median. Leptin correlated better with insulin resistance parameters and had a median variance explained as 33.29%. For morphometric measures of obesity, the median was 16%.[30] Among the morphometric measures, BMI, WHR, WC and TF did not differ significantly from each other in terms of explaining variance in insulin resistance.

Not all studies report R^2 values in the published paper. We requested authors of 35 such papers to give us access to their raw data so that we could calculate the coefficients. Of the 35 published studies, four data sets from two research groups could be accessed from whose data we could calculate 16 correlations out of which 13 R^2 values were below the median (chi square = 6.25, $p = 0.01$). If the median without leptin was considered, 12 of 16 were below the median (chi square = 4, $p = 0.04$). Thus, correlations in unpublished data seemed to be significantly weaker than the published ones.

Of 164 R^2 values, 157 were accompanied by ethnicity information. The median for these 157 was 20.25%. Studies on populations dominated by east Asian ethnicity had R^2 values significantly below the median (16 below and 4 above the median, chi square = 7.2, $p = 0.007$). In studies from populations dominated by South Americans (7 above and 3 below the median) (chi square = 1.6, $p = 0.2$), south and central Asians (17 below and 17 above the median) (chi square = 0, $p = 1$), Africans (7 below and 2 above the median) (chi square = 2.77, $p = 0.095$) and Caucasoid-dominated populations (American, European and Australian white) (32 below and 39 above the median, chi square = 0.69, $p = 0.406$), R^2 values were not significantly above or below the median.

The age group under study had a significant effect on the strength of the correlations. R^2 was positively correlated with the midpoint of the age range of the study and more strongly correlated with the width of the age range of the study (Figure 2). This may suggest that obesity is a better predictor of insulin resistance at a later age. Broader age range coverage by itself may strengthen the correlation. There was a positive correlation between age range covered and midpoint of the age range. After correcting for the effect the width of range, the correlation of R^2 with midpoint age became non-significant. Therefore, whether obesity is a better predictor of insulin resistance at a later age is doubtful. The time of publication (calendar year) and sample size did not show significant effects on the variance explained.

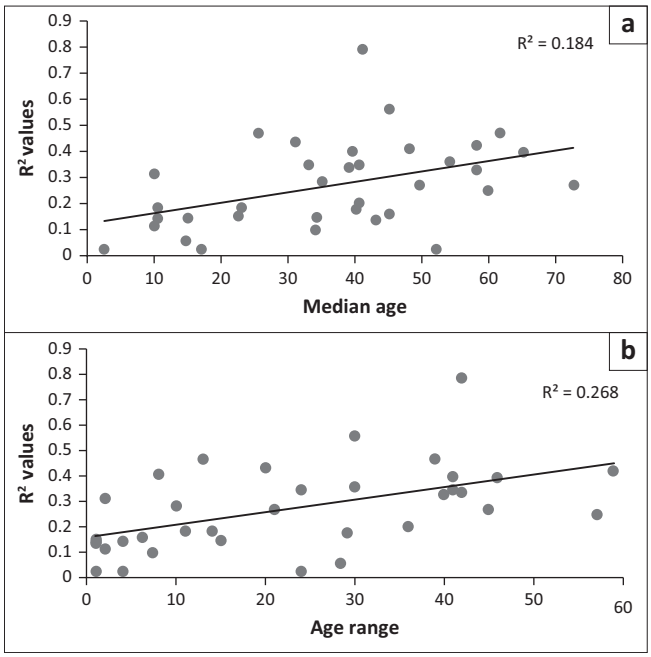

FIGURE 2: Variance in insulin resistance explained by obesity is dependent upon age and age range of the study group. (a) Correlation between mid-point of age range and R^2 for obesity insulin resistance correlation. (b) Correlation between the width of the age range and R^2 for obesity insulin resistance correlation.

Discussion

The frequency distribution of R^2 in the studies indicates that the relationship between obesity and insulin resistance is highly variable across studies, but in the majority, the variance explained is quite poor. Populations dominated by east Asians had poorer R^2 than the global median. A popular interpretation is that in Asians the relationship has a lower intercept and greater slope.[11] This analysis demonstrates that not only the intercept or the slope of the relation is shifted but also the strength of the correlation is itself much weaker. Furthermore, this difference was noted only in east Asians and was lost when all Asian studies were pooled.

Among the various measures of obesity, all morphometric parameters performed poorly. The notion that central obesity is better correlated with insulin resistance[31] was not supported as WHR showed even lower predictive power than BMI across studies. Total body fat was also not a consistently better predictor than BMI. Plasma leptin concentration was a much better predictor of insulin resistance, but the relationship between obesity and plasma leptin concentration is not very straightforward. Although leptin is mainly secreted by adipocytes, expression in other tissues including brain, liver, placenta, gastric mucosa, skeletal muscle and mammary epithelium[32] is known. Leptin expression per unit fat mass is affected by a number of other signals including

behavioural and sex hormone signalling, fasting, glucocorticoids, thyroid hormone, infections, bacterial endotoxins and cytokines.[32] At a given adiposity, stress also affects leptin expression.[33] Many of the factors affecting leptin expression also affect insulin sensitivity. Moreover, leptin expression is known to be stimulated by insulin,[34,35,36] which makes it likely that at least part of the correlation may reflect reverse causation. Therefore, stronger correlation between leptin and insulin resistance cannot be taken to conclusively support the causal role of obesity in insulin resistance.

It is important to note that among the studies that had not published the R^2 values, but whose raw data were accessible, the majority of R^2 values were below the global median. This suggests that there is likely to be a publication bias against reporting low or non-significant correlations. Removing the publication bias may lower the median further.

Overall, in the majority of the studies, both morphometric and biochemical measures of obesity seem to explain only a small part of the variation in insulin resistance. This suggests that there can be other causal factors for insulin resistance independent of obesity. In experimental physiology, a number of signals have been demonstrated that affect insulin sensitivity independent of obesity.[13,14,15,16] In epidemiological data, factors other than obesity such as socioeconomic status[37] or individual behaviour[38,39] are significantly associated with insulin resistance or T2DM. A number of pathways linking behaviour to insulin signalling are reviewed by Watve.[40] In evolutionary medicine, the classical 'thrift' family of hypotheses have recently received much criticism[41] and a number of alternative hypotheses for the origins of insulin resistance have been suggested that are not necessarily obesity dependent. They include fertility selection hypothesis of Corbett et al.[42] and behavioural switch hypothesis of Watve and Yajnik.[43] A number of hypotheses about intrauterine programming also do not involve obesity as a primary cause of insulin resistance. They include the fast life-cycle hypothesis[44] or mechanistic target of rapamycin (mTOR) over-activation hypothesis.[45] The causal relationship between obesity and insulin resistance is also debated. James Neel, the father of thrifty gene hypothesis, did not consider obesity as a cause of type 2 diabetes.[46] In models of intrauterine growth retardation, hyperinsulinaemia is shown to appear before insulin resistance[47] and it is possible that hyperinsulinaemia is primary, which leads to insulin resistance on the one hand and obesity on the other. Thus, a number of alternative possibilities exist, but currently, we know little about them because they have not been sufficiently explored.

Our analysis reveals the limited role of obesity and thereby highlights the importance of investigating alternative possibilities. A possible clinical implication of our finding is that obesity control will have only a limited success in preventing type 2 diabetes. More research needs to be focused on the other possible causes of insulin resistance and their importance at the clinical level. Any effort in this direction can be extremely enlightening and useful for the prevention, control and treatment of type 2 diabetes.

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Competing interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

Authors' contributions

H.B.V. and M.G.W. designed the study. H.B.V. did the search. H.B.V. and M.G.W. did the screening and analysis and wrote the article.

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Appendix starts on the next page →

Appendix 1: Sixty-three studies used to identify the inclusion and exclusion criteria

1. Abate N, Chandalia M, Snell P, Grundy S. Adipose Tissue Metabolites and Insulin Resistance in Nondiabetic Asian Indian Men. J Clin Endocrinol Metab. 2004 Jun;89(6):2750–5.
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