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CHAPTER 3

Insulin resistance in patients with type 1 diabetes assessed by glucose clamp studies: systematic review and meta-analysis

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Submitted

ABSTRACT

Aim: The aim of this study was to perform a systematic review and meta-analysis on the presence and degree of insulin resistance in adult patients with type 1 diabetes mellitus compared to healthy controls, assessed by hyperinsulinemic euglycemic clamp studies.

Methods: We conducted a systematic search of publications using PubMed, EMBASE, Web of Science, and COCHRANE Library from their inception to December 1st, 2013.

Hyperinsulinemic euglycemic clamp studies comparing adult patients with type 1 diabetes mellitus to healthy controls were eligible. Data extraction was independently performed by two investigators, using a standardized data extraction sheet. Primary outcome measures were pooled mean differences of insulin sensitivity of endogenous glucose production (EGP), of glucose uptake and of lipolysis reflected by levels of non-esterified fatty acids (NEFA). We estimated mean (standardized) differences and 95% confidence intervals (95% CI) using random effects meta-analysis.

Results: We included 38 publications in this meta-analysis, involving a total of 522 patients and 689 healthy controls. Overall, the risk of bias in the included studies was limited. The weighed mean differences in EGP during hyperinsulinemia between patients and controls was 0.88 (95% CI: 0.47, 1.29) in the basal state and 0.52 (95% CI: 0.09, 0.95) in insulin stimulated conditions, indicating decreased insulin-mediated suppression of EGP in diabetic patients compared to controls. Insulin sensitivity of glucose uptake was either reported as M value (M), glucose infusion rate (GIR), glucose disposal rate (GDR) or metabolic clearance rate (MCR). Weighed mean differences were similar for M -3.98 (95% CI: -4.68, -3.29), and GIR -4.61, (95% CI: -5.86,-3.53). Weighed mean difference for GDR was -2.43 (95% CI: -3.03, -1.83) and -3.29 (95% CI: -5.37, -1.22) for MCR, indicating decreased peripheral insulin sensitivity in patients with type 1 diabetes mellitus. Insulin mediated inhibition of lipolysis was decreased in patients with type 1 diabetes mellitus, reflected by increased levels of NEFA in the basal state and clamp steady state.

Conclusions: Insulin resistance is a prominent feature of patients with type 1 diabetes mellitus and involves hepatic, peripheral and adipose tissues.

3

INTRODUCTION

Although type 1 diabetes mellitus is characterized by absolute insulin deficiency, type 1 diabetes is also associated with insulin resistance (1;2). Insulin resistance is defined as a decreased biological response to a certain concentration of insulin. Impaired insulin action has been described in both poorly and adequately controlled patients with type 1 diabetes mellitus (3;4), although the degree of insulin resistance varies substantially between patients (2;5). In patients with type 1 diabetes mellitus, insulin resistance is an important risk factor for development of micro-and macrovascular complications (5;6). Cardiovascular disease is still the leading cause of mortality in these patients (7). Therefore, it is important to understand the relation between insulin resistance and type 1 diabetes mellitus.

The hyperinsulinemic euglycemic clamp method, first described by DeFronzo et al, is considered the reference standard for measurement of basal and insulin-stimulated insulin sensitivity under a variety of circumstances (8). Using isotope tracers, tissue specific insulin sensitivity can be quantified (9). Briefly, insulin is infused intravenously at a constant rate in a subject after an overnight fast. Glucose is 'clamped' at a predetermined level (euglycemic clamp glucose ~ 5 mmol/L or isoglycemic at basal glucose levels) by titrating a variable glucose infusion rate. As a consequence of hyperinsulinemia, glucose uptake in skeletal muscle and adipose tissue is increased, whereas lipolysis and endogenous glucose production are suppressed. Under steady state conditions, the rate of glucose infusion equals the rate of glucose uptake by peripheral tissues. The degree of insulin resistance is inversely related to the amount of glucose necessary to maintain euglycemia. Endogenous glucose production can be calculated using isotope tracers of glucose and insulin resistance is reflected by increased endogenous glucose production during a certain degree of hyperinsulinemia. Increased lipolysis, as a consequence of insulin resistance, results in increased levels of non-esterified fatty acids (NEFA). In summary, insulin resistance is characterized by decreased glucose uptake and increased endogenous glucose production and NEFA levels.

Our aim was to perform a systematic review and meta-analysis on insulin resistance in adult patients with type 1 diabetes mellitus compared to healthy controls, assessed by hyperinsulinemic clamp studies.

METHODS

DATA SOURCES AND SEARCHES

In collaboration with a trained librarian, a search string was composed. The following databases were searched from their inception to December 1st, 2013: PubMed, EMBASE, Web of Science, and COCHRANE Library. The search strategy consisted of the combination of three concepts:

1. Glucose clamp technique
2. Type 1 diabetes
3. Insulin resistance

For these three items, relevant keyword variations were used, which included keyword variations in the controlled vocabularies of the various databases, and also free text word variations. The search strategy was optimized for all consulted databases, taking into account differences of controlled vocabularies as well as differences of database-specific technical variations. The reference lists of all potentially relevant articles were screened for additional publications. The search was restricted to English language (see Appendix A for details of the literature search).

STUDY SELECTION

Experimental studies using the hyperinsulinemic, iso- or euglycemic clamp technique comparing adult patients with type 1 diabetes mellitus and healthy controls were eligible.
We excluded studies in patients with renal and/or pancreatic transplantations, since immune suppressive drugs are known to induce insulin resistance. Studies performed in children and adolescents were beyond the scope of this review.

DATA EXTRACTION AND RISK OF BIAS ASSESSMENT

Data extraction was performed independently by 2 investigators (E.D. and J.A.R.) using a standard data-extraction sheet. In case of disagreement, consensus was reached after discussion with a third reviewer (O.D).
Insulin sensitivity parameters were extracted as provided in the included studies. Information at the study level was extracted on 1) patient characteristics (age, gender, mean duration of diabetes, body mass index (BMI), insulin treatment, mean daily insulin use, HbA1c values), 2) clamp characteristics (including type of glucose clamp technique, use of stable isotopes, 3) type of outcome measure (endogenous glucose production (EGP), glucose disposal rate (GDR, M), glucose infusion rate (GIR), metabolic clearance rate (MCR) and levels of non-esterified free fatty acids (NEFA)).
In case authors compared one control group to two groups of patients with type 1 diabetes mellitus, (i.e. poor vs well regulated diabetes), data of this control group were used twice in this meta-analysis. If necessary, values were recalculated to the international system units, i.e. mmol/L for glucose and pmol/L for insulin.

Assessment of risk of bias was based on study components that could potentially bias the association between insulin resistance and type 1 diabetes mellitus. The following components were considered: 1) Adequacy of the clamp protocol. The clamp protocol was considered adequate in case predetermined fixed insulin dose and predetermined steady state glucose levels were described and sampling of blood glucose levels was performed at brief intervals throughout the experiment. Furthermore, the duration of insulin infusion and the clamp should be described. 2) Adequacy of steady state in insulin-stimulated phase of glucose clamp study. Calculations of insulin sensitivity parameters are based on the assumption that in steady state, glucose infusion equals glucose uptake. Studies were considered to have a low risk of bias in case duration of steady state, steady state insulin and glucose levels were reported and stable during steady state in both patients and controls. Studies that did not report steady state values for glucose and insulin were scored as unclear. 3) Inclusion of patients with poorly regulated diabetes, defined as an HbA1c level>9%. Chronic hyperglycemia is known to increase insulin resistance (10) and, therefore, insulin resistance could be overestimated in these patients. 4) Presence of impaired glucose tolerance in healthy controls. Studies were considered to have a low risk of bias if healthy controls were reported to have a normal glucose tolerance, tested prior to the study.

DATA SYNTHESIS AND ANALYSIS

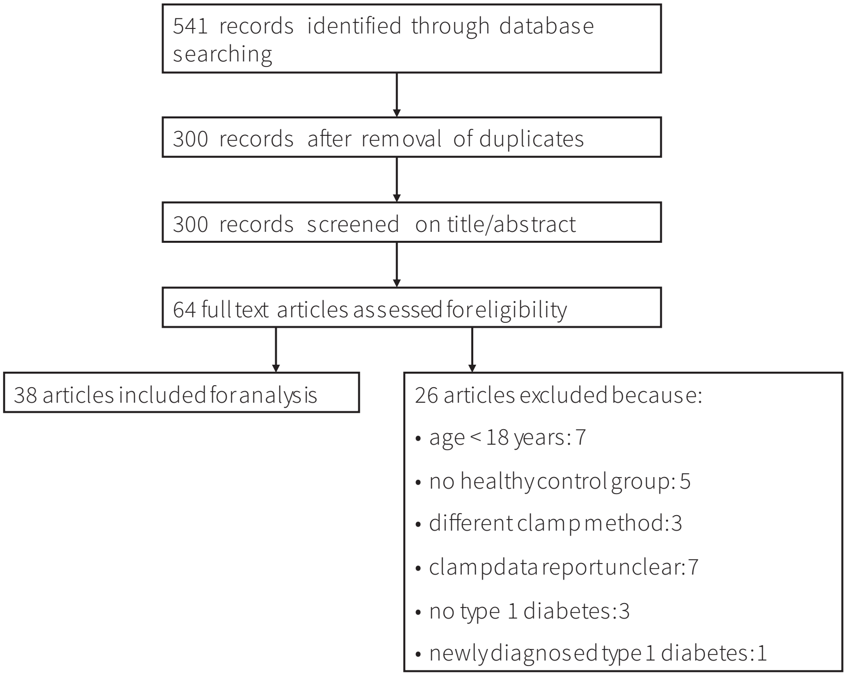
The primary outcome measures in this meta-analysis were pooled mean differences of endogenous glucose production (EGP), peripheral glucose uptake and NEFA levels during hyperinsulinemic euglycemic clamp conditions in patients with type 1 diabetes compared to healthy controls. Parameters for peripheral glucose uptake could be reported as glucose disposal rate (GDR), M-value (M), glucose infusion rate (GIR) or metabolic clearance rate (MCR). Therefore, we used standardized mean outcome measures for peripheral glucose uptake to allow comparison between studies. Values for EGP, GDR, M and GIR were reported in mg/kg/min and recalculated if necessary when reported in other units. MCR was reported in ml/kg/min and NEFA levels in μmol/L. We performed random effects meta-analysis using (standardized) mean differences and 95% confidence intervals (95% CI). Statistical analyses were performed with STATA Statistical Software (Statacorp, College Station, Texas, USA) version 12.1.

RESULTS

SEARCH RESULTS (FIGURE 1)

The initial search included 300 publications after removal of duplicates and ultimately 64 articles were retrieved for detailed assessment. Publications were excluded for following reasons: no type 1 diabetes mellitus (n=3), age of participants was below 18 years (n=7), absence of a healthy control group (n=5), use of a clamp technique, not comparable to the iso-or euglycemic clamp method (n=3), no quantitative outcome measures reported (n=7) and 1 publication was excluded because participants had newly onset type 1 diabetes mellitus, in whom endogenous insulin production might be partly preserved. Finally, 38 publications were included in this meta-analysis, of which 5 publications (11-15) consisted of two and 1 publication (16) of three studies.

Figure 1. Summary of search results



STUDY CHARACTERISTICS

Study characteristics of included studies are presented in Table 1. In total, 38 publications were included, of which 14 publications used stable isotope tracer infusions for assessment of tissue specific insulin sensitivity (1;3;4;11-45). Mean age of included patients ranged from 22 to 50 years and from 23 to 64 years in healthy controls. BMI ranges in patients (21—28 kg/m^2) and controls (22-29 kg/m^2) were similar. Most clamp studies used the hyperinsulinemic euglycemic clamp method, and only 2 publications performed a hyperinsulinemic isoglycemic clamp. The insulin infusion rates and steady state insulin levels differed considerably between studies, and ranged between 20 and 120 mU/m^2/min for insulin infusion rates and between 160 and 8972 pmol/L for steady state insulin levels. Both patients with short and long duration of disease were included and a large variation in diabetes regulation was present between studies.

Table 1. Study characteristics of the included publications

Characteristic	Patients	Controls
Total participants	522	698
% men	54%	55%
Mean age (yr),	22-50	23-64
Mean BMI (kg/m^2)	21.0-28.3	21.5-28.9
Mean duration of diabetes (yr)	1.2-38.9	NA
Mean daily insulin dose (U/day)	34-61	NA
Mean HbA1c (%)	5.6-14.2	4.8-6.6
Clamp procedure		
• insulin infusion rates clamp ($mU/m^2/min$)	20-120	20-120
• mean glucose levels steady state (mmol/L)	4.0-9.6	4.0-5.5
• mean insulin levels steady state (pmol/L)	167-8972	160-7320

Range of means was reported of included studies

RISK OF BIAS

Risk of bias assessment is summarized in Table 2. Most publications (33 out of 38) reported an adequate clamp protocol. Steady state values and -durations were reported in 32 publications. Twelve publications included patients with a mean HbA1c values >9%. Twenty four publications did not report on impaired glucose tolerance in healthy controls. Overall, the risk of bias in the included publications was considered to be limited.

Table 2. Potential sources of bias

Author	Year	Journal	Isotopes	Steady state	Clamp protocol	Controls without diabetes	Poorly regulated
Baron	1991	JCEM	NO	YES	NO	YES	YES
Bergman	2012	JCEM	YES	YES	YES	NR	NO
Bravard	2011	Diabetes	NR	NR	NO	YES	YES
Brown TL	2012	ADA Conference	NR	NR	NR	NR	NR
DeFronzo	1982	Diabetologia	YES	YES	YES	NR	NR
Del Prato	1983	JCEM	NO	NR	YES	NR	NO
Donga	2013	Diab Metab Research Rev	YES	YES	YES	NR	NO
Ebeling	1998	Diabetologia	NO	YES	YES	NR	NO
Ekstrand	1998	Neprhrol Dial Tra	NO	YES	YES	NR	NO
Fasching	1993	Diabetologia	YES	NR	YES	NR	NO
Greenfield	2002	JCEM	NO	YES	YES	YES	NO
Hother-Nielsen	1987	Diabetologia	YES	YES	YES	NR	NR
Hsu	2011	Plos one	NO	YES	YES	NR	NO
Kacerovsky	2010	J Int Med	NO	YES	YES	NR	NO
Keller	1986	Horm met Res	YES	YES	YES	YES	NO
Kerner	1985	Klin Wochenschr	NO	YES	YES	NR	YES
Kruszynska	1986	Diabetologia	NO	YES	NO	NR	YES
Lager	1983	BMJ	NO	YES	YES	NR	YES
Maahs	2010	Diabetes	NO	YES	YES	NR	NO
Makimattila	1996	JCEM	NO	YES	YES	NR	NO
Makimattila	1996	Circulation	NO	YES	YES	NR	NO
Nijs	1989	Diabetologia	NO	YES	YES	NR	YES
Nijs	1991	Diab Research Clin Pract	NO	YES	YES	YES	YES
Nuutila	1993	Am J Physiol	NO	YES	YES	YES	NO
Pernet	1984	Diabetologia	NO	YES	YES	NR	YES
Pereira	2012	JCEM	NO	YES	YES	NR	NO
Perseghin	2003	Am J Physiol	YES	YES	YES	YES	NO
Perseghin	2005	Diabetologia	YES	YES	YES	YES	NO
Rosenfalck	2006	Diab Med	NO	NO	YES	NR	NO
Schauer	2011	Diabetes	NO	YES	YES	NR	NO
Shay	2012	Diabetic Med	NO	NR	NR	YES	NO
Simonson	1985	Diabetes	YES	YES	YES	YES	YES
Tessari	1986	J Clin Invest	NO	YES	YES	YES	NO
Trevisan	1986	JCEM	YES	YES	YES	NR	NO
Yki-Jarvinen	1984	JCEM	YES	YES	YES	NR	YES
Yki-Jarvinen	1984	JCEM	NO	YES	YES	YES	YES
Yki-Jarvinen	1984	Diabetes Care	YES	YES	YES	YES	NO
Yki-Jarvinen	1986	Acta Endocrinol	NO	YES	YES	YES	YES

NR, not reported

ENDOGENOUS GLUCOSE PRODUCTION (FIGURE 2 AND 3)

From studies using stable isotopes, 10 studies reported data obtained during hyperinsulinemia on basal endogenous glucose production (EGP) and 5 studies on clamp EGP. In the basal state, mean EGP in diabetes patients varied from 2.0 to 4.5 mg/kg/min versus 1.6 to 3.0 mg/kg/min in controls. The weighed mean difference in basal EGP between patients and controls was 0.88 (95% CI: 0.47, 1.29), indicating less suppression of EGP in diabetic patients compared to controls. Under steady state hyperinsulinemic conditions, mean reported EGP values ranged from 0.0 to 1.2 mg/kg/min in diabetes patients and from 0.0 to 0.6 mg/kg/min in controls, with a weighed mean difference of 0.52 (95% CI: 0.09,0.95), compatible with less suppression of EGP under insulin stimulated conditions. This means that EGP during hyperinsulinemia was higher in patients compared to controls, indicating decreased hepatic insulin sensitivity in type 1 diabetes mellitus.

Figure 2. Basal endogenous glucose production

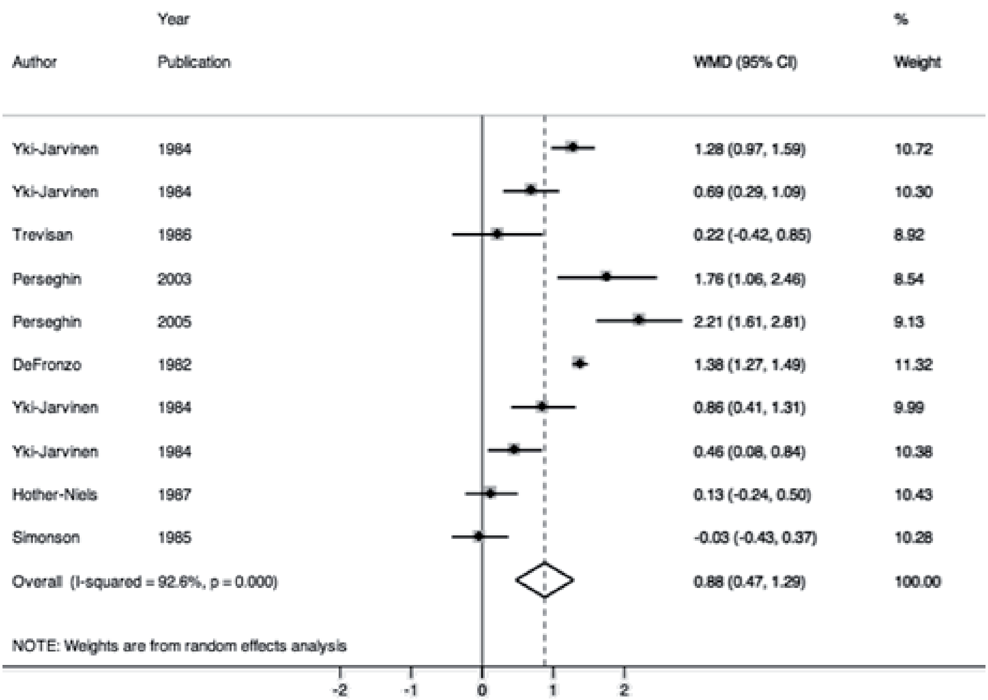
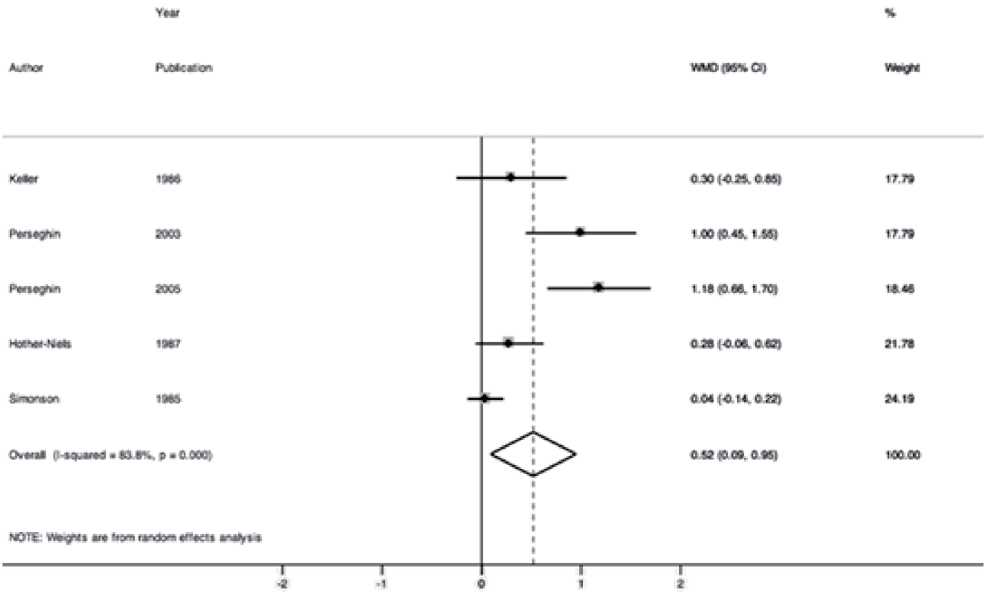


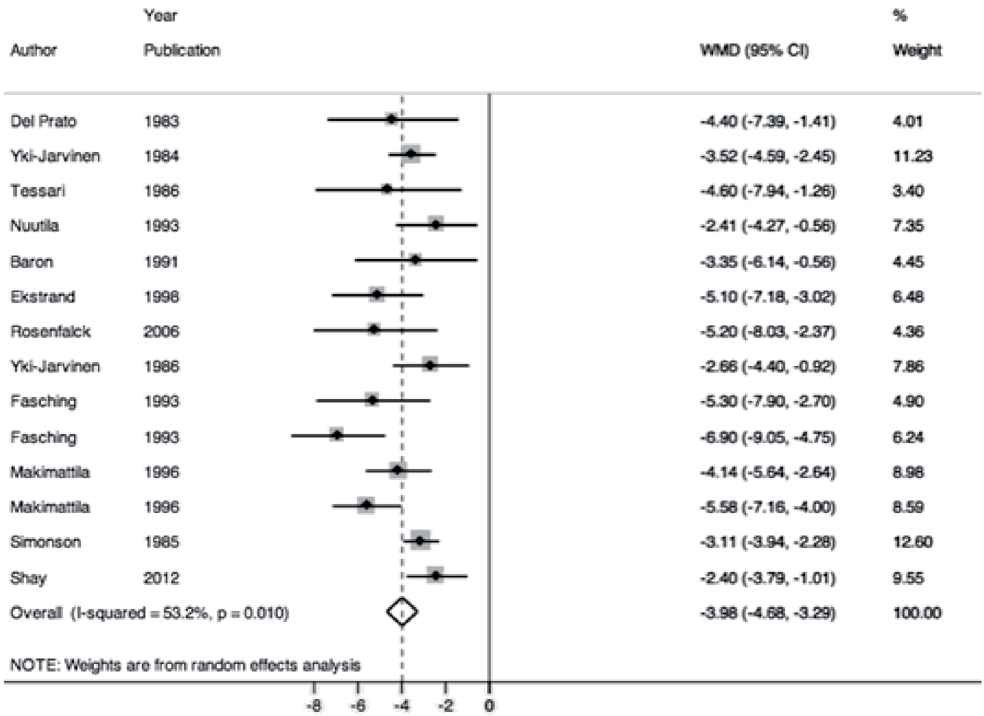
Figure 3. Clamp endogenous glucose production



PERIPHERAL GLUCOSE UPTAKE (FIGURE 4)

M value, glucose infusion rate (GIR), glucose disposal rate (GDR) and metabolic clearance rate (MCR) during hyperinsulinemic clamp conditions are parameters of insulin-mediated glucose uptake. Most clamp studies reported M values (n=14) or GIR (n=15). Mean M values ranged from 3.9 to 9.9 mg/kg/min for diabetic patients and from 7.0 to 14.0 for healthy controls. Mean GIR in patients varied between 2.4 and 8.9 mg/kg/min and in controls between 4.2 and15.6 mg/kg/min . Weighed mean difference for M was -3.98 (95% CI: -4.68, -3.29), in accordance with the weighed mean difference in GIR (-4.61, (95% CI: -5.86,-3.53)). The weighed mean difference for GDR was -2.43 (95% CI: -3.03, -1.83) and weighed mean difference for MCR was -3.29 (95% CI: -5.37, -1.22). All values indicate decreased peripheral glucose uptake under insulin stimulated conditions, indicating decreased peripheral insulin sensitivity in patients with type 1 diabetes compared to healthy controls.

Figure 4. Peripheral glucose uptake: M value



LIPOLYSIS AND LEVELS OF NON-ESTERIFIED FATTY ACIDS (NEFA) (FIGURES 5 AND 6)

Eleven studies reported data on basal NEFA levels and 9 studies reported NEFA levels during clamp conditions. In the basal state, mean NEFA levels ranged from 473 to 1220 μmol/L in patients and 370 to 860 μmol/L in healthy controls. NEFA levels during clamp conditions ranged from 20 to 380 μmol/L in patients and 10 to 390 μmol/L in controls. Weighed mean difference for basal NEFA levels between patients and controls was 134 (95%CI: 7, 261) and for clamp NEFA levels 24 (95% CI: 1, 47) . This reflects decreased inhibition of lipolysis in patients with type 1 diabetes mellitus, and the values obtained during standardized hyperinsulinemic conditions indicate decreased insulin sensitivity of lipolysis.

Figure 5. Basal non-esterified fatty acids (NEFA) levels

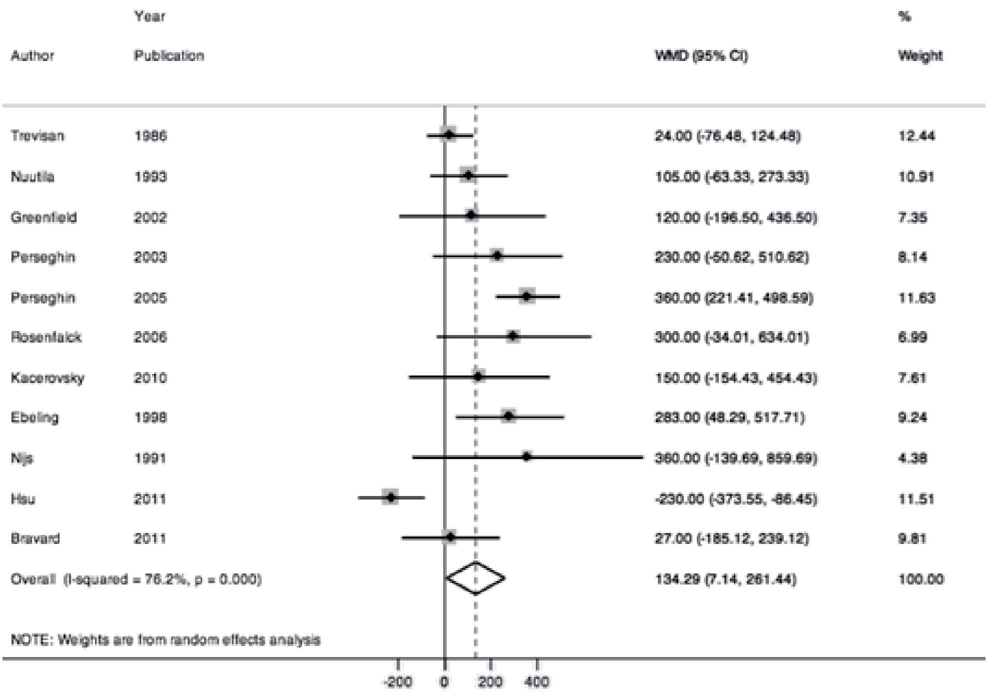
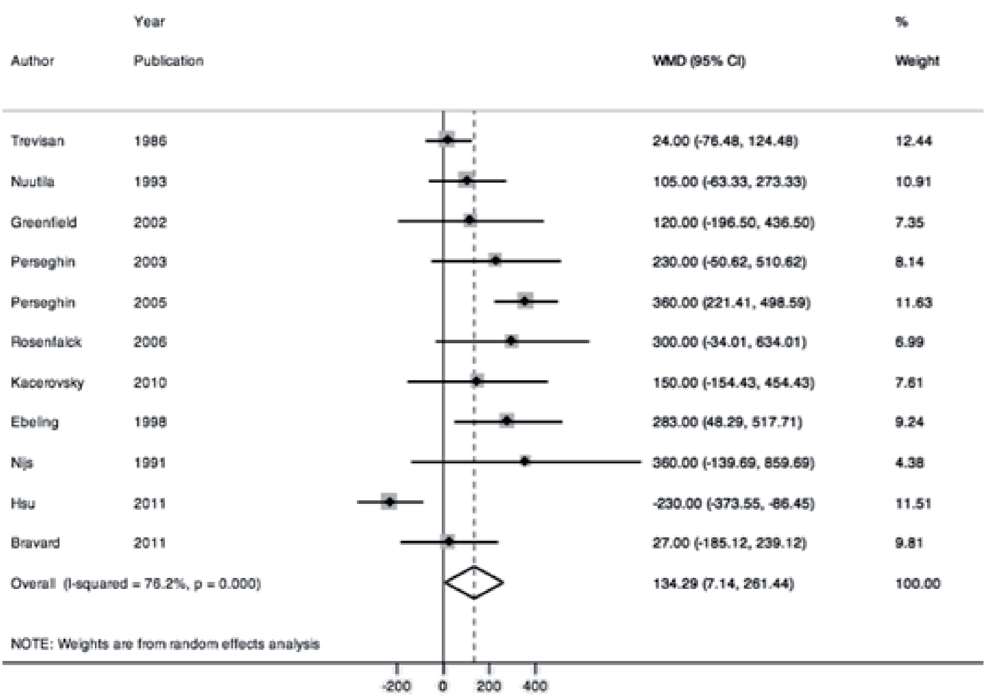


Figure 6. Clamp non-esterified fatty acids (NEFA) levels



DISCUSSION

In this meta-analysis, we compared insulin resistance between patients with type 1 diabetes mellitus and healthy controls using data from hyperinsulinemic euglycemic clamp studies. The present meta-analysis shows that insulin resistance is a prominent feature of patients with type 1 diabetes mellitus which involves hepatic, peripheral and adipose tissues. This association is consistent and present in both poorly and well regulated patients.

Major strengths of this meta-analysis are the relatively large number of included publications and the large number of included participants, 522 patients and 698 controls. A limitation of this meta-analysis is the potential for confounding. For instance, in patients with type 1 diabetes recent hyperglycemia or hypoglycemia preceding the clamp study could have negatively influenced clamp outcome measures on insulin sensitivity (46;47). Furthermore, the use of certain drugs is associated with decreased insulin sensitivity. For example, beta blockers and calcium channel antagonist are known to alter autonomic nervous system activity and decrease insulin sensitivity (48). In this meta-analysis, some publications excluded subjects who were using these drugs, whereas other publications did not report on the use of medication. Nonetheless, although we cannot completely exclude confounding, the findings from the included clamp studies are all very similar and consistently indicate decreased insulin sensitivity in multiple tissues in patients with type 1 diabetes mellitus. Clamp protocols differed substantially between included publications, although all studies refer to the same original study design by DeFronzo et al (8). For instance, the insulin infusion rates and duration of the clamp procedures varied considerably, which resulted in a wide range of steady state insulin levels in the included clamp studies. Therefore, differences in insulin sensitivities found between clamp studies can be partly explained by different steady state levels of insulin. To allow comparison between studies, we only included publications directly comparing patients with type 1 diabetes mellitus with healthy controls.

In both clinical practice and clinical research, little attention is paid to insulin resistance as a common feature of type 1 diabetes mellitus. In contrast to studies in patients with type 2 diabetes mellitus, data on the effect of lifestyle factors on insulin sensitivity in type 1 diabetes mellitus are sparse (49). Although previous studies have assessed the relation between insulin resistance and development of cardiovascular complications, only a few studies are available on improving insulin resistance in type 1 diabetes mellitus. For example, Rosenfalck et al reported that a low fat diet during 3 months improved peripheral insulin sensitivity by 30% in patients with type 1 diabetes (39). A twelve week exercise program in adolescents with type 1 diabetes mellitus improved insulin sensitivity by 23%, although this was not reflected in HbA1c levels (50). However, these studies looked at short term outcome measures and were not designed to investigate the relation between improvement of insulin sensitivity in type 1 diabetes mellitus and prevalence of cardiovascular complications. Conversely, insulin resistance can be readily increased in patients with type 1 diabetes by only a single night of partial sleep deprivation (51). These intervention studies indicate that insulin resistance is not a fixed pathophysiological condition in patients with type 1 diabetes.

The pathophysiological basis of insulin resistance in multiple tissues in patients with type 1 diabetes is most likely to be complex. Different concepts have been introduced to explain the presence of insulin resistance in subgroups of patients with type 1 diabetes. The term “double diabetes” was introduced for patients with type 1 diabetes, with a family history of type 2 diabetes who have a higher risk to develop components of type 2 diabetes at some age (52). This notion of “double diabetes” should be differentiated from the accelerator concept, which proposes that autoimmune diabetes is triggered by factors like BMI and insulin resistance. However, neither of these two concepts fully explains the observations of the current meta-analysis, since the included studies were not merely obtained in subgroups of patients with type 1 diabetes. Rather, insulin resistance seems to reflect a general phenomenon in patients with type 1 diabetes mellitus. Nonetheless, it is possible that certain conditions in subgroups with type 1 diabetes including genetic factors and life style may exacerbate insulin resistance in patients with type 1 diabetes.

In conclusion, type 1 diabetes mellitus is characterized by both insulin deficiency and insulin resistance in multiple metabolic pathways. Therefore, studies are warranted to assess if interventions aimed at reducing insulin resistance provide clinical benefits in patients with type 1 diabetes mellitus.

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