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Insulin clearance is different in men and women

Michael D. Jensen¹, Soren Nielsen², Nidhi Gupta¹, Rita Basu¹, and Robert Rizza¹

¹Endocrine Research Unit, Mayo Clinic, Rochester, Minnesota

²Medical Department M, Aarhus University Hospital, Aarhus C, Denmark

Abstract

Objective—Insulin is often infused based upon total body weight (TBW) or fat free mass (FFM) for glucose clamp protocols. We observed greater insulin concentrations in men than women using this approach and examined whether splanchnic insulin extraction accounts for the differences.

Materials/Methods—Whole body insulin clearance was measured during a pancreatic clamp study (somatostatin to inhibit islet hormone secretion) including 13 adults (6 men) and whole body insulin clearance was measured during a euglycemic, hyperinsulinemic clamp study including 27 adults (13 men). Femoral artery and hepatic vein blood samples were collected to measure splanchnic insulin balance. For the pancreatic clamp study insulin was infused at rates of 0.5, 1.0, and 2.0 mU•kgTBW⁻¹•min⁻¹ and for the euglycemic, hyperinsulinemic clamp study insulin was infused at 2.5 mU•kg FFM⁻¹•min⁻¹.

Results—Significantly greater arterial insulin concentrations were found in men than women. Splanchnic plasma flow was similar in men and women in both protocols. Splanchnic insulin extraction and the fraction of infused insulin removed by splanchnic bed were significantly greater in men than in women. However, whole body insulin clearance was greater in women than men.

Conclusions—Infusing insulin per body weight or FFM results in higher plasma insulin concentrations in men than women. Splanchnic insulin extraction is greater in men, indicating greater peripheral insulin clearance in women accounts for the sex differences we observed. This finding has implications for insulin clamp study design and raises the question of which tissues take up more insulin in women.

Keywords

insulin; splanchnic extraction; hyperinsulinemic clamp

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Corresponding author: Michael D. Jensen, M.D., Mayo Clinic, Endocrine Research Unit, 200 1st St SW, Rm 5-194 Joseph, Rochester, Minnesota 55905, Tel: 507-255-6515, Fax: 507 255-4828, jensen@mayo.edu.

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Disclosures

None.

Author Contributions

MDJ: data collection and analysis, data interpretation and manuscript writing. SN: data collection and analysis, data interpretation and manuscript writing. NG: data interpretation and manuscript writing. RB: data collection and analysis, data interpretation and manuscript writing. RR: data collection and analysis, data interpretation and manuscript writing.

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Introduction

Hyperinsulinemic, euglycemic clamp protocols are employed to measure the effects of a given insulin concentration on metabolic variables independent of changes in glucose concentrations. To obtain the desired insulinemia, insulin is infused intravenously at rates that are typically adjusted for total body weight (TBW), body surface area, or fat free mass (FFM) in order to allow for inter individual differences in volume of distribution [1]. When examining some of our previously published data on insulin dose response characteristics for FFA suppression [2], we noted that plasma insulin concentrations were greater in men than in women. This could have been due to errors in compounding, using FFM as opposed to TBW as a way to calculate the infusion rate, or due to differences in insulin clearance between men and women. Given that the liver clears a relatively large fraction of secreted insulin and that we have conducted a number of euglycemic, hyperinsulinemic clamp studies of splanchnic metabolism, we took the opportunity to query these data sets to determine whether differences in insulin clearance during an insulin clamp between men and women can be attributed to differential insulin uptake across the splanchnic bed.

Although previous studies have examined insulin secretion in different pathophysiological conditions [3–5], few have measured regional insulin extraction in humans [6]. We could find no data regarding potential differences in splanchnic insulin extraction in men and women. In the basal state, approximately 40–80% of insulin released from the pancreas is thought to be extracted by the splanchnic region (mainly liver) [7, 8]. Therefore, differences in splanchnic insulin clearance between men and women appeared to be the most likely explanation as to why we find that men have greater insulin concentrations than women in response to the same insulin infusion rates.

Research Design and Methods

Volunteers

Mayo Clinic Institutional Review Board approved this study and informed written consent was obtained from all participants. Non-diabetic volunteers were recruited for these studies. We used stored plasma samples from a previously published pancreatic clamp study [9] in order to measure insulin clearance under conditions of somatostatin-suppressed endogenous insulin secretion. Arterial and hepatic vein samples were available from 6 men (age 62 ± 11 years; BMI 27 ± 2 kg/m²) and 7 women (age 61 ± 7 years; BMI 30 ± 8 kg/m²) to measure insulin concentrations. The euglycemic, hyperinsulinemic clamps study (without somatostatin) included 13 men (age 35 ± 7 years; BMI 29 ± 6 kg/m²) and 14 women (age 29 ± 6 years; BMI 28 ± 7 kg/m²). All participants were weight stable for at least 3 months prior to the study and all had a normal blood cell count and biochemistry panel. Because of the demographics of the Rochester, MN population, all of the participants in these studies were Caucasian. None of the volunteers smoked tobacco and none of the women were using oral contraceptives. The women participating in the pancreatic clamp study were post-menopausal and the women participating in the euglycemic, hyperinsulinemic clamp study were pre-menopausal.

Protocol

Body composition was measured using DXA (Lunar Radiation, Madison, WI) and the fat free mass (FFM) data from DXA was used to calculate the insulin infusion rate for the euglycemic hyperinsulinemic clamp study. Pre-study dietary and physical activity protocols for these Clinical Research Unit (CRU) studies were as previously described [10]. In brief, volunteers receive meals (50–55% carbohydrate, 30% fat, 15–20% protein) from the metabolic kitchen for 3 days before the study. Participants were admitted to the CRU the

evening before the study, ingested their standard meal between 1730 and 1800 h and then fasted (with the exception of water) until the completion of study. An 18-gauge intravenous catheter was placed in a forearm vein that evening and kept patent with a saline infusion.

The following morning participants were transferred to the Vascular Radiology Laboratory at ~ 0800, where femoral arterial and hepatic venous catheters were placed as previously described [11]. The volunteers were then transferred back to the CRU for remainder of the study.

Insulin (*Humulin insulin, Lilly, Indianapolis, IN*) and indocyanine green (Cardio-Green, Becton, Dickinson, and Cockeysville) were used in these studies.

Pancreatic clamp study—As previously described [9], this protocol was a three-step, hyperinsulinemic, hyperglycemic clamp where insulin was infused relative to TBW rather than FFM. At 1000 h (time 0) infusions somatostatin ($72 \text{ ng} \cdot \text{kg TBW}^{-1} \cdot \text{min}^{-1}$; Bachem California, Torrance, CA) and replacement doses of glucagon ($0.65 \text{ ng} \cdot \text{kg TBW}^{-1} \cdot \text{min}^{-1}$, Eli Lilly, Indianapolis, IN) and growth hormone ($3.0 \text{ ng} \cdot \text{kg TBW}^{-1} \cdot \text{min}^{-1}$; Genentech, South, San Francisco, CA) were started and continued throughout the study period ($t = 0$ –420 min). Also at time 0 minutes an infusion of insulin ($0.5 \text{ mU} \cdot \text{kg TBW}^{-1} \cdot \text{min}^{-1}$) was begun. After 180 min the insulin rate was increased to $1.0 \text{ mU} \cdot \text{kg TBW}^{-1} \cdot \text{min}^{-1}$ (180–300 min) and then to $2.0 \text{ mU} \cdot \text{kg TBW}^{-1} \cdot \text{min}^{-1}$ (300–420 min). Plasma glucose was measured in duplicate every 5–10 min (Beckman Instruments, Palo Alto, CA) and clamped at ~9.3 mmol/L (165 mg/dL) using 50% dextrose. Femoral artery and hepatic vein blood samples were obtained at 10 min intervals during the last 30 minutes of each insulin infusion period for measurement hormone, substrate and indocyanine green concentrations [9]. From the samples remaining from original 14 non-diabetic participants, [9], there was sufficient remaining plasma to remeasure insulin concentrations in 13.

Euglycemic, hyperinsulinemic clamp study—A 2-hour hyperinsulinemic, euglycemic clamp employing a primed, continuous insulin infusion at a rate of $2.5 \text{ mU} \cdot \text{kg FFM}^{-1} \cdot \text{min}^{-1}$ was performed. Plasma glucose was measured in duplicate every 5–10 min (Beckman Instruments, Palo Alto, CA) in order to adjust the glucose infusion rate. Plasma glucose was clamped at ~5 mmol/L (90 mg/dl) using 50% dextrose.

Assays

Arterial and hepatic vein plasma indocyanine green concentrations were measured on the day of the study using a spectrophotometer. Blood was sampled prior to the infusion to construct the indocyanine green calibration curve. Insulin concentrations were measured using chemiluminescent sandwich assays (Sanofi Diagnostics Pasteur, Chaska, MN). All hepatic and arterial samples for each study were run in same assay and all men and women samples in same assay in order to avoid confounding effects of variations in assay results.

Calculations

Splanchnic plasma flow (SPF, ml/min) was calculated by dividing the indocyanine green infusion rate ($\mu\text{g}/\text{min}$) by the arterial-hepatic venous concentration difference of the dye ($\mu\text{g}/\text{ml}$).

Insulin clearance rates are presented in their unadjusted form in order to avoid drawing spurious conclusions [12]. Splanchnic insulin extraction (SIE, $\mu\text{U}/\text{min}$) was calculated as:

$$\text{SIE} = \text{SPE} \times (\text{FA insulin} - \text{HV insulin})$$

where, FA insulin and HV insulin are the concentrations of insulin ($\mu\text{U/ml}$) in the femoral arterial and hepatic venous plasma, respectively.

Splanchnic insulin clearance (SIC, ml/min) was calculated as:

$$\text{SIC} = \frac{\text{SIE}}{\text{FA insulin}}$$

Fractional splanchnic insulin extraction (%), the fraction of infused insulin that was taken up by the splanchnic bed was calculated as:

$$\text{Fractional SIE} = \frac{\text{SIE}}{I_R} \times 100$$

Where, I_R is the insulin infusion rate ($\mu\text{U/min}$).

Assuming near complete suppression of endogenous insulin secretion, whole body insulin clearance (WBIC, ml/min) could be calculated for those in P2 as:

$$\text{WBIC} = \frac{I_R}{\text{FA insulin}}$$

Statistics

All data are presented as mean $\pm$ SD. All variables were normally distributed (by Kolmogorov-Smirnov test for normality). Student's t-test was used to compare the values in males and females. The within group dose response effect of insulin on splanchnic insulin handling was evaluated using one-way ANOVA and Scheffe's post-hoc test. A $p < 0.05$ was considered statistically significant. JMP (version 7.0; SAS Institute; Cary, NC) was used for the analysis. Relationships between insulin clearance and body fat as well as insulin clearance and insulin action with respect to glucose disposal were tested using linear regression analysis.

Results

Volunteer characteristics

The volunteer characteristics are provided in Table 1. The expected differences in body fat and FFM were present for participants in both protocols.

Plasma insulin concentrations

In both protocols, arterial insulin concentrations were significantly greater in men than women (Table 2); however, hepatic vein insulin concentrations were not significantly different between the two groups. As expected, arterial insulin concentration increased as a function of insulin infusion rate in the pancreatic clamp study (repeated measures ANOVA; $p < 0.001$).

Splanchnic plasma flow

Splanchnic plasma flow was similar in men and women during the euglycemic hyperinsulinemic, clamp: 962 ± 92 vs. 912 ± 51 ml/min. Likewise, in the pancreatic clamp study splanchnic plasma flow was not different in men and women, although it was less than

in hyperinsulinemic clamp study because of the somatostatin infusion: (step 1) 702 ± 37 vs. 687 ± 95 ml/min; (step 2) 759 ± 49 vs. 687 ± 81 ml/min; (step 3) 760 ± 43 vs. 720 ± 69 ml/min (all $P = \text{NS}$).

Insulin extraction and clearance

Because somatostatin suppressed endogenous insulin secretion for the pancreatic clamp study, we could assess whole body clearance of infused insulin. Insulin clearance was significantly less in men than women during the first insulin step (1379 ± 40 vs 1709 ± 133 mL/min, respectively, $p < 0.05$) and the third insulin step (1237 ± 57 vs 1558 ± 125 , respectively, $p < 0.05$), and during the second insulin step, although the sex-difference was of the same magnitude, it did not meet our criteria for statistical significance (1361 ± 63 vs. 1644 ± 142 , men vs. women, $p=0.10$) (Figure 1, panel A).

Contrary to our hypothesis, the fraction of infused insulin that was removed by the splanchnic bed was significantly greater in men than in women during the 0.5 (44 ± 8 vs. $34 \pm 8\%$ $p < 0.05$), 1.0 (49 ± 8 vs. $35 \pm 7\%$, $P < 0.001$), and 2.0 $\text{mU} \cdot \text{kg TBW}^{-1} \cdot \text{min}^{-1}$ insulin infusion rates (53 ± 6 vs. $39 \pm 10\%$, $P < 0.05$). Splanchnic insulin extraction ($\mu\text{U}/\text{min}$) was significantly different in both groups even after adjusting for age, BMI and percent body fat. Splanchnic clearance (mL/min) of infused insulin (Figure 1, panel B) was somewhat greater in men than women, although the differences were not statistically significant.

The whole body clearance of infused insulin during the euglycemic, hyperinsulinemic clamp study was 1985 ± 103 and 2711 ± 255 ml/min in men and women, respectively ($P = 0.01$).

Insulin clearance was not correlated with body fat or percent body fat in men, women or the combined group.

Discussion

We unexpectedly found sex-related differences in plasma insulin concentrations as we examined previously published data from hyper insulinemic clamp studies where we infused insulin relative to FFM [2]. This is unlikely to have been a compounding error, because we found similar sex differences in other experiments such as those reported here. In hindsight we published, but did not appreciate or comment on, the same sex differences in insulin concentrations in a large study that did not include hepatic vein sampling [13]. Herein we report the same pattern of sex -differences in plasma insulin concentrations when insulin is infused relative to TBW and FFM- arterial plasma insulin concentrations are significantly greater in men than women. The lower insulin concentrations at the same infusion rate indicate greater whole body clearance of infused insulin in women. We hypothesized this greater whole body clearance would be due to greater splanchnic clearance of infused insulin in women. Instead, we found that men removed a significantly greater proportion of infused insulin in the splanchnic bed than women and had somewhat greater splanchnic insulin extraction than women.

We have reported that there are sex differences in leg blood flow [14], meal fatty acid metabolism [15, 16] and free fatty acid metabolism [17, 18], but no differences with respect to glucose metabolism [17]. The finding of sex differences in insulin clearance was unexpected, especially in light of reports that insulin clearance is not different in men and women of European [19] and Hispanic [20] origin. One study [19] compiled data from volunteers who were studied using an insulin infusion rate of $1 \text{ mU} \cdot \text{kg TBW}^{-1} \cdot \text{min}^{-1}$, an approach similar to ours, but each of the 20 different research centers involved used their own insulin assay. In contrast, all samples from these studies were analyzed in the same

assay. The other investigators infused insulin relative to surface area [20], which may affect comparisons between men and women (see below).

Insulin clearance is a complex process involving multiple organs and cells, including liver, kidney, adipose and muscle tissues, fibroblasts, and gastrointestinal cells [21]. The liver is thought to be the primary site for insulin clearance, removing approximately 40–80% during the first portal passage [22]. The factors that modulate hepatic insulin uptake include prolonged increases in portal insulin levels (reduced clearance) [23] and variations in splanchnic plasma flow [23]. We note that the data are inconsistent since both a reduced [24] and unchanged [25] splanchnic insulin extraction have been reported in relation to an increase in splanchnic plasma flow; splanchnic plasma flow was not different between men and women in our study. Other factors that may alter hepatic insulin clearance include increased hepatic FFA delivery [26, 27] and insulin resistance [28]. However, it is not possible to examine whether insulin clearance is correlated with insulin stimulated glucose disposal because insulin concentrations are used in both the dependent and independent variables, which violates the assumptions of regression analysis.

Kidney is another major site for insulin clearance from the systemic circulation accounting for approximately 50% of C-peptide and 10–30% of insulin extraction [29, 30]. Though, some previous groups [31] have investigated the changes in renal extraction of insulin under different pathophysiological conditions (for example, following a glucose meal), the process is incompletely understood. All insulin-sensitive cells are involved in clearance and degradation of the insulin not cleared by liver and kidney. Muscle [21] and adipose tissue [32] [33] may contribute to insulin clearance, however, limited relevant data are available and this issue needs to be researched further. Given that women have less muscle than men it would seem unlikely muscle is the source of greater insulin clearance for women. Might the greater fat mass in females account for the greater peripheral insulin clearance? We would expect the sex differences in insulin delivery to adipose tissue to be relatively small given the relatively low adipose tissue blood flow rates [34, 35]. Using these values the average total adipose tissue blood flow would be 411 and 529 mL/min in men and women, respectively. Not only is this small difference unlikely to account for the large difference in peripheral clearance, men have more visceral fat than women, and visceral fat is reported to be more active at degrading insulin than subcutaneous fat [33]. Finally, we observed no association between body fat and total or non-splanchnic insulin clearance in men, women or the combined group. Unfortunately, because adipose tissue is widely dispersed throughout the body it is difficult to assess regional clearance using A-V sampling techniques to more directly address this issue. Given the relative importance of the kidney in insulin clearance and the relatively easy accessibility, comparing renal insulin clearance in men and women would seem to be the next logical step to understand the sex differences we observed.

Although in some cases insulin action can be expressed as a dose response (change in metabolic response relative to change in insulin concentration) for each individual [2], in other cases it is necessary to achieve comparable plasma insulin concentrations in each volunteer. We suggest that our data may be used to adjust the insulin infusion rates for men and women separately in order to achieve more similar insulin concentrations.

We used data from our studies where insulin was infused relative to FFM or TBW. Some investigators infuse insulin relative to body surface area, which they might argue would overcome the issues we encountered when infusing per FFM or TBW. However, within the typical range of height observed in our most studies of adults, body weight is the major contributor to body surface area as calculated using height and weight. For example, whereas the insulin infusion rates in men and women participating in the pancreatic clamp

study were virtually identical whether per TBW or per surface area. The same is not true when insulin is infused relative to FFM, however. The insulin infusion rate of $2.5 \text{ mU} \cdot \text{kg FFM}^{-1} \cdot \text{min}^{-1}$ used in our euglycemic, hyperinsulinemic clamp study resulted in insulin infusion rates of 76 ± 1 and $61 \pm 1 \text{ mU} \cdot \text{m}^2 \cdot \text{min}^{-1}$ in men and women, respectively. Although using the per m^2 approach to data may create problems at times [12], this tactic likely will create lesser differences in plasma insulin concentrations between men and women than will the use of FFM to calculate infusion rates.

We acknowledge limitations to our results. Although we observed significant differences in total insulin clearance and the fraction of insulin cleared by the splanchnic bed between men and women, we cannot identify which tissues account for these differences. In addition, the exaggerated magnitude of the difference between men and women during the euglycemic, hyperinsulinemic clamp study may have been related to using FFM instead of TBW to calculate the insulin dose. In addition, because all of our volunteers were Caucasian we cannot extrapolate with certainty to other ethnic groups. An offsetting strength is the novel data regarding splanchnic insulin clearance in persons who received somatostatin to inhibit endogenous insulin secretion, thereby assuring accurate systemic and splanchnic clearance values.

In summary, we found that whole body insulin clearance of infused insulin is greater in women than men. In contrast, splanchnic extraction of infused insulin is significantly greater in men than in women. This finding has implications for the design of insulin clamp studies. Sex specific considerations must be taken into account when infusing insulin relative to TBW or FFM if the goal is to achieve equal insulin concentrations in men and women; using FFM to calculate insulin infusion amounts will result in substantially greater insulin concentrations in men than women.

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Abbreviations

TBW	total body weight
FFM	fat free mass
BMI	body mass index
DXA	dual energy x-ray absorptiometry
CRU	Clinical Research Unit
SPF	splanchnic plasma flow
SIE	splanchnic insulin extraction
SIC	splanchnic insulin clearance

FA	femoral artery
HV	hepatic vein
WBIC	whole body insulin clearance
I_R	insulin infusion rate
SD	standard deviation
ANOVA	analysis of variance

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Figure 1.

Panel A depicts whole body clearance of infused insulin (ml/min) in men and women participating in the pancreatic clamp study, which employed a somatostatin infusion to suppress endogenous insulin secretion. Panel B depicts the splanchnic clearance of infused insulin (ml/min) in men and women participating in both the euglycemic, hyperinsulinemic clamp protocol and pancreatic clamp protocol. The dose of insulin in the euglycemic, hyperinsulinemic clamp protocol is 2.5 mU·kg FFM⁻¹·min⁻¹ and for the pancreatic clamp study the doses of insulin were 0.5, 1.0 and 2.0 mU·kg TBW⁻¹·min⁻¹. Values are mean ± SD; * p<0.05 vs. men. Splanchnic insulin clearance was not significantly different between men and women.

Table 1

Descriptives

	Hyperinsulinemic clamp		Pancreatic clamp	
	Men (n=13)	Women (n=14)	Men (n=6)	Women (n=7)
Age (years)	35 ± 7	29 ± 6 [*]	62 ± 11	61 ± 7
BMI (kg/m ²)	29 ± 6	28 ± 7	27 ± 2	30 ± 8
% Body fat	26 ± 7	38 ± 9 [‡]	28 ± 6	36 ± 9
Fat free mass (kg)	64 ± 7	47 ± 6 [‡]	57 ± 5	37 ± 5 [‡]

Mean ± SD;

^{*}
p<0.05,[‡]
p<0.001 vs. men

Table 2

Plasma insulin concentrations

Insulin Infusion rate	Arterial		P value	Hepatic Vein	
	Men	Women		Men	Women
Hyperinsulinemic clamp					
2.5 mU•kg FFM ⁻¹ •min ⁻¹	84 ± 22	47 ± 15	< 0.001	26 ± 17	19 ± 8
Pancreatic clamp					
Step 1: 0.5 mU•kg TBW ⁻¹ •min ⁻¹	32 ± 2	23 ± 5	< 0.001	4 ± 2	3 ± 1
Step 2: 1.0 mU•kg TBW ⁻¹ •min ⁻¹	64 ± 6	48 ± 10	< 0.001	10 ± 4	7 ± 3
Step 3: 2.0 mU•kg TBW ⁻¹ •min ⁻¹	142 ± 14	99 ± 17	< 0.001	23 ± 8	17 ± 4

Values are given as mean ± SD. Insulin concentrations are in μU/ml. FFM - Fat free mass; TBW - Total body weight. The P values refer to the comparisons between arterial insulin concentrations for men and women. Arterial and hepatic vein insulin concentrations increased significantly during each step of the pancreatic clamp. Hepatic vein insulin concentrations were not different between men and women.