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Insulin clearance is different in men and women

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ABSTRACT

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. 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/kg of TBW per minute; and for the euglycemic, hyperinsulinemic clamp study, insulin was infused at 2.5 mU/kg of FFM per minute. 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. 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 that 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.

1. Introduction

Hyperinsulinemic, euglycemic clamp protocols are used 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) to allow for interindividual 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, 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

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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 (SIE) in men and women. In the basal state, approximately 40% to 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 (SIC) 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.

2. Research design and methods

2.1. Volunteers

The Mayo Clinic Institutional Review Board approved this study, and informed written consent was obtained from all participants. Nondiabetic volunteers were recruited for these studies. We used stored plasma samples from a previously published pancreatic clamp study [9] to measure insulin clearance under conditions of somatostatin-suppressed endogenous insulin secretion. Arterial and hepatic vein (HV) samples were available from 6 men (age, 62 ± 11 years; body mass index [BMI], 27 ± 2 kg/m^2) and 7 women (age, 61 ± 7 years; BMI, 30 ± 8 kg/m^2) to measure insulin concentrations. The euglycemic, hyperinsulinemic clamps study (without somatostatin) included 13 men (age, 35 ± 7 years; BMI, 29 ± 6 kg/m^2) and 14 women (age, 29 ± 6 years; BMI, 28±7 kg/m^2). All participants were weight stable for at least 3 months before 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 white. None of the volunteers smoked tobacco, and none of the women were using oral contraceptives. The women participating in the pancreatic clamp study were postmenopausal; and the women participating in the euglycemic, hyperinsulinemic clamp study were premenopausal.

2.2. Protocol

Body composition was measured using dual-energy x-ray absorptiometry (Lunar Radiation, Madison, WI); and the FFM data from dual-energy x-ray absorptiometry were used to calculate the insulin infusion rate for the euglycemic hyperinsulinemic clamp study. Prestudy 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 5:30 and 6:00 PM, 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 approximately 8:00 AM, where femoral arterial and hepatic venous catheters were placed as previously described [11]. The volunteers were then transferred back to the CRU for the remainder of the study.

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

2.3. Pancreatic clamp study

As previously described [9], this protocol was a 3-step, hyperinsulinemic, hyperglycemic clamp where insulin was infused relative to TBW rather than FFM. At 10:00 AM (time 0), infusions of somatostatin (72 ng/kg TBW per minute; Bachem California, Torrance, CA) and replacement doses of glucagon (0.65 ng/kg TBW per minute, Eli Lilly, Indianapolis, IN) and growth hormone (3.0 ng/kg TBW per minute; Genentech, South, San Francisco, CA) were started and continued throughout the study period (t = 0-420 minutes). In addition, at time 0 minute, an infusion of insulin (0.5 mU/kg TBW per minute) was begun. After 180 minutes, the insulin rate was increased to 1.0 mU/kg TBW per minute (180-300 minutes) and then to 2.0 mU/kg TBW per minute (300-420 minutes). Plasma glucose was measured in duplicate every 5 to 10 min (Beckman Instruments, Palo Alto, CA) and clamped at approximately 9.3 mmol/L (165 mg/dL) using 50% dextrose. Femoral artery and HV blood samples were obtained at 10-minute intervals during the last 30 minutes of each insulin infusion period for measurement of hormone, substrate, and indocyanine green concentrations [9]. From the samples remaining from original 14 nondiabetic participants, [9], there was sufficient remaining plasma to remeasure insulin concentrations in 13.

2.3.1. Euglycemic, hyperinsulinemic clamp study

A 2-hour hyperinsulinemic, euglycemic clamp using a primed, continuous insulin infusion at a rate of 2.5 mU/kg FFM per minute was performed. Plasma glucose was measured in duplicate every 5 to 10 minutes (Beckman Instruments) to adjust the glucose infusion rate. Plasma glucose was clamped at approximately 5 mmol/L (90 mg/dL) using 50% dextrose.

2.4. Assays

Arterial and HV plasma indocyanine green concentrations were measured on the day of the study using a spectrophotometer. Blood was sampled before 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 the same assay, and all men and women samples were run in the same assay to avoid confounding effects of variations in assay results.

2.5. Calculations

Splanchnic plasma flow (SPF, milliliters per minute) was calculated by dividing the indocyanine green infusion rate

(micrograms per minute) by the arterial-hepatic venous concentration difference of the dye (micrograms per milliliter).

Insulin clearance rates are presented in their unadjusted form to avoid drawing spurious conclusions [12]. Splanchnic insulin extraction (microunits per minute) was calculated as follows:

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

where FA insulin and HV insulin are the concentrations of insulin (microunits per milliliter) in the femoral arterial and hepatic venous plasma, respectively. Splanchnic insulin clearance (milliliters per minute) was calculated as follows:

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

Fractional SIE (percentage), the fraction of infused insulin that was taken up by the splanchnic bed, was calculated as follows:

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

where I_R is the insulin infusion rate (microunits per minute).

Assuming near-complete suppression of endogenous insulin secretion, whole-body insulin clearance (WBIC, milliliters per minute) could be calculated for those in *P2* as follows:

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

2.6. Statistics

All data are presented as mean ± SD. All variables were normally distributed (by Kolmogorov-Smirnov test for normality). Student *t* test was used to compare the values in male and female subjects. The within-group dose-response effect of insulin on splanchnic insulin handling was evaluated using 1-way analysis of variance and Scheffe post hoc test. $P < .05$ 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.

Table 1 – Descriptives

	Hyperinsulinemic clamp		Pancreatic clamp	
	Men (n = 13)	Women (n = 14)	Men (n = 6)	Women (n = 7)
Age (y)	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
FFM (kg)	64 ± 7	47 ± 6†	57 ± 5	37 ± 5†

Mean ± SD.
* $P < .05$ vs men.
† $P < .001$ 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 per minute	84 ± 22	47 ± 15	<.001	26 ± 17	19 ± 8
Pancreatic clamp					
Step 1: 0.5 mU/kg TBW per minute	32 ± 2	23 ± 5	<.001	4 ± 2	3 ± 1
Step 2: 1.0 mU/kg TBW per minute	64 ± 6	48 ± 10	<.001	10 ± 4	7 ± 3
Step 3: 2.0 mU/kg TBW per minute	142 ± 14	99 ± 17	<.001	23 ± 8	17 ± 4

Values are given as mean ± SD. Insulin concentrations are in microunits per milliliter. The *P* values refer to the comparisons between arterial insulin concentrations for men and women. Arterial and HV insulin concentrations increased significantly during each step of the pancreatic clamp. Hepatic vein insulin concentrations were not different between men and women.

3. Results

3.1. 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.

3.2. Plasma insulin concentrations

In both protocols, arterial insulin concentrations were significantly greater in men than women (Table 2); however, HV insulin concentrations were not significantly different between the 2 groups. As expected, arterial insulin concentration increased as a function of insulin infusion rate in the pancreatic clamp study (repeated-measures analysis of variance; $P < .001$).

3.3. 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, SPF was not different in men and women, although it was less than that in the 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*s = not significant).

3.4. 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; $P < .05$) and the third insulin step (1237 ± 57 vs 1558 ± 125, respectively; $P <$

.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; $P = .10$) (Fig. 1A).

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% ± 8%; $P < .05$), 1.0-(49% ± 8% vs 35% ± 7%; $P < .001$), and 2.0-mU/kg TBW per minute insulin infusion rates (53% ± 6% vs 39% ± 10%; $P < .05$). Splanchnic insulin extraction (microunits per minute) was significantly different in both groups even after adjusting for age, BMI, and percentage body fat. Splanchnic clearance (milliliters per minute) of infused insulin (Fig. 1B) was somewhat greater in men than women, although the differences were not statistically significant.

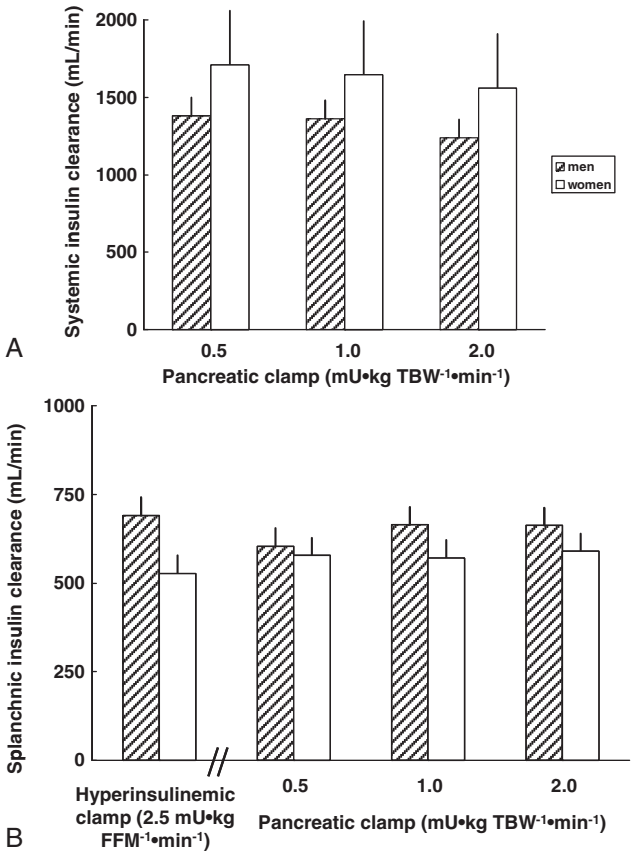

Fig. 1 – A, Whole-body clearance of infused insulin (milliliters per minute) in men and women participating in the pancreatic clamp study, which used a somatostatin infusion to suppress endogenous insulin secretion. B, Splanchnic clearance of infused insulin (milliliters per minute) in men and women participating in both the euglycmic, hyperinsulinemic clamp protocol and the pancreatic clamp protocol. The dose of insulin in the euglycmic, hyperinsulinemic clamp protocol is 2.5 mU/kg FFM per minute; and for the pancreatic clamp study, the doses of insulin were 0.5, 1.0, and 2.0 mU/kg TBW per minute. Values are mean ± SD; *P < .05 vs men. Splanchnic insulin clearance was not significantly different between men and women.

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 ($P = .01$).

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

4. Discussion

We unexpectedly found sex-related differences in plasma insulin concentrations as we examined previously published data from hyperinsulinemic 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 HV 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 that 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 SIE 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 mU/kg TBW per minute, 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 the 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% to 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 SPF [23]. We note that the data are inconsistent because both reduced [24] and unchanged [25] SIEs have been reported in relation to an increase in SPF; SPF 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% to 30% of insulin extraction [29,30]. Although some previous groups [31] have investigated the changes in renal extraction of insulin under different pathophysiological conditions (eg, 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 that muscle is the source of greater insulin clearance for women. Might the greater fat mass in women 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 nonsplanchnic 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 arterio-venous 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 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 most of our 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 however not true when insulin is infused relative to FFM. The insulin infusion rate of 2.5 mU/kg FFM per minute used in our euglycemic, hyperinsulinemic clamp study resulted in insulin infusion rates of 76 ± 1 and 61 ± 1 mU · m^2 · min^{-1} in men and women, respectively. Although using the per-square-meter 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. 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 white, we cannot extrapolate with certainty to other ethnic groups. An offsetting strength is the novel data regarding SIC in persons who received somatostatin to inhibit endogenous insulin secretion, thereby ensuring accurate systemic and splanchnic clearance values.

In summary, we found that WBIC 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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Conflict of Interest

The authors have no conflicts of interest to disclose.

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