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Insulin Resistance in ICU Patients: Women Have Stronger Metabolic Response

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Abstract: Glycaemic control (GC) has been associated with improved outcomes in critically ill patients. However, inter- and intra- patient metabolic variability significantly increase the risk of hypoglycaemia when using insulin to control glycaemia. Model-based protocols often identify key physiological parameters from patient data, and demonstrated safe and effective GC. Based on recent studies showing gender difference in insulin secretion, this study uses retrospective data to identify whether there exists a difference in sexes in metabolic stress response, and thus in how personalised GC is given.

Retrospective data from 145 ICU patients under GC who started GC in the first 12 hours of ICU stay are used. Insulin sensitivity (SI) is identified hourly, as well as the hour-to-hour percentage change in SI (%ΔSI). Differences between males and females SI and %ΔSI over 6-h blocks are compared using hypothesis and equivalence testing. A difference in SI levels would suggest a difference in metabolic stress response to insult, while a difference in %ΔSI levels would suggest a resulting difference in the difficulty to control.

Results show females are significantly more insulin resistant than males and not equivalent, suggesting stronger stress response to insult induced stress. Metabolic variability is equivalent in both groups, advocating GC safety and efficacy should be similar between males and females, despite potential higher insulin rates required for females.

This study is the first to suggest potential gender differences in the metabolic stress response.

Keywords: Glycaemic control, Insulin, Insulin resistance, Insulin Sensitivity, Metabolic variability

1. INTRODUCTION

Increased insulin resistance and excessive glucose production are common responses to severe injury in intensive care unit (ICU) patients (McCowen *et al.*, 2001), causing abnormal elevated blood glucose (BG) concentrations associated with increased morbidity and mortality (Krinsley, 2003). Glycaemic control (GC), using insulin therapy to reduce BG levels to safer ranges, is thus essential for these patients. While everyone agrees GC should be used to control glycaemia below the renal glycosuria threshold (10.0 mmol/L or 180 mg/dL), the optimal target band remains a debate (Chase *et al.*, 2017; Gunst *et al.*, 2016; Krinsley, 2018; Preiser *et al.*, 2016).

Many studies showed improved outcomes associated with lower, normoglycaemic, ranges (Chase *et al.*, 2008b; Krinsley, 2004; Reed *et al.*, 2007; Van den Berghe *et al.*, 2001). However, many others failed to replicate the results (Brunkhorst *et al.*, 2008; Finfer *et al.*, 2009; Finfer *et al.*, 2012; Preiser *et al.*, 2009). Chase (Chase *et al.*, 2010) provided an analysis indicating GC had to be achieved for virtually all patients to show potential benefit, which many studies failed to do. A later study showed inter- and intra-patient variability and its evolution made this goal hard to achieve safely and effectively (Chase *et al.*, 2011b; Pretty *et al.*, 2012). In particular, the associated increased risk of hypoglycaemia due to patient variability in the response to insulin when targeting lower ranges being potentially more harmful than beneficial. Thus, guidelines now recommend targeting higher, broader ranges and thus permissive hyperglycaemia (Krinsley, 2018; Singer *et al.*, 2019).

More recently, independent studies have introduced new considerations. Patient-specific, model-based GC protocols have shown that safe and effective control for all patients is possible, despite targeting lower ranges (Mesotten *et al.*, 2017; Stewart *et al.*, 2016). Those ranges are associated with improved outcomes (Krinsley *et al.*, 2015; Penning *et al.*, 2014; Penning *et al.*, 2015; Signal *et al.*, 2012). Typically, these methods use key identified, patient-specific physiological parameters to dose insulin (Chase *et al.*,

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2011a). They can thus better account for inter- and intra-patient metabolic variability (Chase *et al.*, 2019; Chase *et al.*, 2018), the main factor making GC hard to achieve safely.

More specifically, it has been shown GC is not a function of severity of patient condition, patient metabolic condition or diabetes status, or outcome, suggesting all patients should benefit given equal quality of control (Uyttendaele *et al.*, 2017). Protocol design is thus the determining factor in GC, where poorly designed protocols with demonstrated low compliance have wrongly blamed lower glycaemic targets for increased hypoglycaemia (Uyttendaele *et al.*, 2019b). Safe, effective control must thus be achieved for all patients before making conclusions on the clinical impact of GC.

Given survivors and non-survivors have been shown to be equally controllable due to having equivalent metabolic variability (Uyttendaele*, et al.*, 2017), it is possible other parameters could influence control if differences in patient-specific metabolic stress response existed. In particular, studies have reported differences in insulin resistance, insulin secretion, glucose effectiveness, and endogenous glucose production, between genders (Basu *et al.*, 2006; Geer *et al.*, 2009; Soeters *et al.*, 2007). In neonatal ICU infants, girls were found to be more insulin resistant than boys given their higher endogenous insulin secretion (Dickson *et al.*, 2015a; Dickson *et al.*, 2015b).

This study examines whether differences in insulin resistance and its variability also exist in adult ICU patients, and if it has an impact on control difficulty.

2. METHODS

2.1 Patient Cohort

Retrospective clinical data from 371 patients on Specialised Relative Insulin Nutrition Tables (SPRINT) GC (Chase*, et al.*, 2008b) are used. Only 145 patients (91 males, 54 females) who started GC within 12h of ICU admission and received insulin for >24h are used. Demographics are in Table 1.

Differences in age, mortality, severity of injury, ICU length of stay, diabetes, and GC outcomes between males and females are not significant. Only median BG levels achieved are significantly different, but this difference is small and does not have any clinical impact (Uyttendaele*, et al.*, 2017).

2.2 Model-based Insulin Sensitivity (SI)

Insulin sensitivity (SI) is a physiological parameter, reflecting patient metabolic response to insulin and glucose, and, thus, patient metabolic stress response. In this study, patient-specific model-based SI is identified hourly, using a clinically validated physiological model (Lin *et al.*, 2011), schematically represented in Fig. 1. This model has been used in the Stochastic Targeted (STAR) GC framework, providing high quality of control for all patients (Evans *et al.*, 2012; Stewart*, et al.*, 2016). The model describes all the metabolic glucose-insulin pharmacodynamics. SI is identified from clinical BG, insulin, and nutrition data using integral based methods (Docherty *et al.*, 2012).

Table 1. Demographic data of male and female sub-cohorts from 145 SPRINT patients.

	Males	Females	P-val
# patients	91	54	
Age	67 [57, 77]	67 [58, 74]	0.63a
Mortality	18%	19%	1.0b
APACHE II score	20 [16, 27]	19.5 [17, 26]	0.98a
First day SOFA score	6 [4, 8]	5.5 [4, 8]	0.46a
ICU length of stay (h)	108 [67, 188]	127.2 [64, 213]	0.91a
SPRINT duration (h)	83 [46, 157]	87 [39, 167]	0.81a
Type 2 Diabetes (%)	13 (14%)	11 (20%)	0.4b
Cohort BG (mmol/L)	5.6 [4.9, 6.6]	5.9 [5.0, 6.9]	<0.01a
Median BG (mmol/L)	5.7 [5.2, 6.1]	6.0 [5.3, 6.4]	0.06a
%BG 4.4-8.0 mmol/L	83 [72, 90]	82 [67, 89]	0.3a
%BG < 4.0mmol/L	1.4 [0, 5.5]	1.4 [0, 6.9]	0.42a
%BG < 2.2mmol/L	0 [0, 0]	0 [0, 0]	/
BG measures/day	15.8 [14.4, 17.5]	15.7 [14.5, 18.2]	0.47a
Median insulin (U/h)	3 [2, 3]	3 [2, 3]	0.26a
Median feed (g/h)	3.5 [2.1, 5.5]	2.8 [1.8, 3.9]	<0.01a
Median feed (%GF)	51 [30, 80]	51 [30, 75]	0.61a
Goal Feed (g/h)	6.5 [6.5, 7.4]	5.2 [5.2, 5.7]	<0.01a

Data is given as per-patient median [IQR] where appropriate. P-values are computed using Wilcoxon Ranksum test (a) or Fisher exact test (b).

Difficulty in control is assessed using the hour-to-hour change in SI levels (%ΔSI), reflecting metabolic variability and thus hyper- and hypo- glycaemic risk. In STAR, metabolic variability is used to assess risk for any given treatment, and to determine the optimal treatment (Evans*, et al.*, 2012; Lin *et al.*, 2008; Uyttendaele *et al.*, 2018; Uyttendaele *et al.*, 2019a).

It is important to note a difference in SI level between males and females would suggest potential difference in metabolic stress response to injury. However, a difference in %ΔSI would suggest an outcome or resulting difference in the difficulty to control these patient cohorts.

2.3 Protocol Comparison and Analyses

This study analyses patient-specific SI and %ΔSI using 6-h blocks over the first 72h of control. Hypothesis testing is used to determine whether the null hypothesis of males and females sub-cohorts being drawn from distributions of equal medians against the alternative they are not can be rejected ($p<0.05$). Due to large data sample size effect, bootstrapping is used (Motulsky, 2014). Resampled cohorts of the same size of the original cohort are created, where sample are randomly chosen with replacement 1000 times, and the differences in median bootstrapped SI or %ΔSI between males and females are computed. If the 95% CI of these differences does not include zero (difference of equal medians = 0), the null hypothesis can be rejected ($p<0.05$). Because it is not clear whether data is independent, the Bonferroni correction for multiple comparison is also considered, where the 12 comparisons made suggest a significance level of $p=0.004$. Therefore, in this case, the 99.6% CI of differences is considered.

Although a difference can be statistically significant, it may not have a significant clinical impact (Motulsky, 2014, 2015). Equivalence testing is thus used to assess if a difference between genders, statistically significant or not, has the potential to change clinical decision-making. The equivalence range used is based on the change in SI required to exceed one standard deviation of BG measurement error (±9.4%) or cause a change in model-based insulin recommendations. This equivalence range thus corresponds to a change in SI of approximately ±15%, based on the median SI value. Further details are published in (Uyttendaele, *et al.*, 2017). If the 95% CI (or 99.6% CI using the Bonferroni correction) of the % difference in medians of bootstrapped cohorts falls within the equivalence range, the difference in distributions can be considered equivalent (Motulsky, 2014). A statistically significant difference can thus well be within equivalence range, suggesting the difference is not sufficient to cause major clinical impact.

Table 2. SI levels comparison between male and female cohorts using 6-h blocks.

Hours	Male Cohort SI (×e-4)	Female Cohort SI (×e-4)	[95%CI] difference in bootstrapped median SI (×e-5)
Day 1			
0-5	1.5 [0.5, 2.7]	1.3 [0.5, 2.3]	[0.0, 4.8]
6-11	2.2 [1.3, 3.7]	1.8 [0.7, 3.3]	**[0.8, 6.6]**
12-17	3.1 [1.7, 4.8]	2.2 [1.1, 4.2]	**[5.3, 13.1]**[a]
18-23	3.3 [1.8, 5.9]	2.4 [1.5, 3.9]	**[4.8, 12.1]**[a]
Day 2			
24-29	3.3 [1.8, 5.7]	2.8 [1.6, 4.0]	**[1.2, 11.0]**
30-35	3.7 [2.1, 6.5]	2.7 [1.8, 4.6]	**[4.8, 14.1]**[a]
36-41	3.6 [2.0, 6.0]	2.8 [1.7, 4.3]	**[2.4, 14.3]**[a]
42-47	3.6 [2.0, 6.0]	2.9 [1.8, 4.2]	**[2.3, 11.1]**[a]
Day 3			
48-53	4.0 [2.2, 6.8]	2.9 [1.9, 4.4]	**[6.4, 15.9]**[a]
54-59	4.4 [2.4, 6.7]	3.2 [1.9, 4.8]	**[4.3, 15.5]**[a]
60-65	3.8 [2.3, 6.0]	3.2 [2.1, 4.6]	**[1.3, 9.7]**
66-71	3.8 [2.5, 5.7]	3.0 [2.4, 4.7]	**[4.1, 11.8]**[a]

Difference in bootstrapped median SI levels is significant (bold) if the 95% CI does not include the null hypothesis value of 0 (p<0.05). [a]Difference remains significant after Bonferroni correction (p<0.004). SI units: L/mU/min.

Table 3. %ΔSI levels comparison between male and female cohorts using 6-h blocks.

Hours	Male Cohort %ΔSI (%)	Female Cohort %ΔSI (%)	[95%CI] difference in bootstrapped median %ΔSI (%)
Day 1			
0-5	4.5 [-23.1, 61.3]	1.6 [-34.5, 51.1]	[-9.7, 9.8]
6-11	7.2 [-12.7, 38.7]	9.9 [-15.4, 42.0]	[-9.7, 4.0]
12-17	5.4 [-10.6, 27.4]	4.5 [-16.3, 37.6]	[-8.3, 7.5]
18-23	2.9 [-15.5, 24.2]	2.4 [-14.6, 25.0]	[-4.7, 7.1]
Day 2			
24-29	2.5 [-12.5, 22.1]	4.7 [-13.0, 24.9]	[-6.9, 1.4]
30-35	0.2 [-15.6, 23.7]	5.6 [-12.0, 24.5]	**[-11.0, -0.7]**
36-41	1.2 [-11.4, 16.2]	0.3 [-17.0, 16.4]	[-3.4, 6.5]
42-47	2.0 [-12.3, 19.8]	0.6 [-11.9, 18.2]	[-3.7, 5.1]
Day 3			
48-53	2.7 [-8.6, 16.3]	0.7 [-10.8, 18.7]	[-2.8, 5.4]
54-59	-0.8 [-15.0, 13.1]	1.3 [-10.2, 18.1]	[-5.8, 1.9]
60-65	1.3 [-11.0, 17.5]	4.5 [-10.0, 19.6]	[-8.0, 0.3]
66-71	1.9 [-9.6, 13.6]	1.6 [-9.0, 14.3]	[-5.3, 3.4]

Difference in bootstrapped median %ΔSI levels is significant (bold) if the 95% CI does not include the null hypothesis value of 0 (p<0.05).

3. RESULTS

SI level comparison for every 6-h block and resulting 95% CI difference in median bootstrapped SI values are presented in Table 2. Equivalence testing results are shown in Fig. 1.

Female SI is lower, and the difference with male is statistically significant (p<0.05) for every 6-h block (95% CI does not include the null hypothesis value 0). These differences generally remain significant using the Bonferroni correction (p<0.004). The difference in SI is also never within equivalence range. Women thus have significantly lower SI, and the difference are not within equivalent range, suggesting it has a clinical impact on decision making.

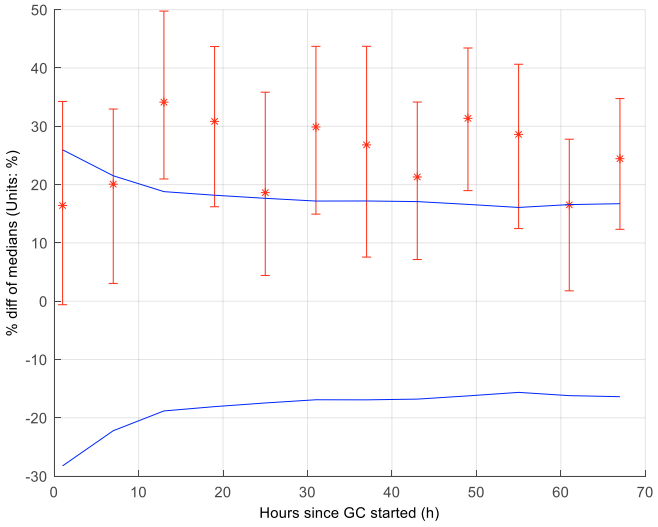

Fig. 1. Equivalence testing results on SI between males and females for each 6-h block. Blue solid lines give equivalence range. Equivalence accepted if 95% CI of percentage difference in bootstrapped median SI values is within equivalence range, and rejected otherwise.

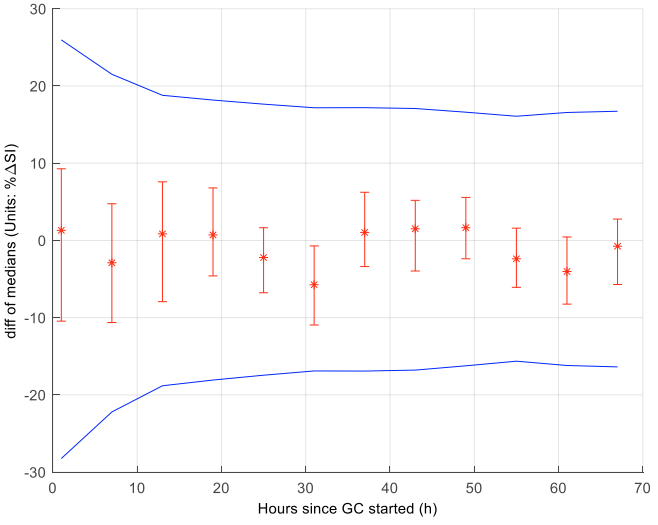

Fig. 2. Equivalence testing results on %ΔSI between males and females for each 6-h block. Blue solid lines give equivalence range. Equivalence accepted if 95% CI of percentage difference in median bootstrapped %ΔSI values is within equivalence range, and rejected otherwise.

Considering metabolic variability, %ΔSI comparison for every 6-h block and resulting 95% CI difference in median bootstrapped %ΔSI values are in Table 3. Equivalence testing results are shown in Fig. 2.

Differences in metabolic variability (%ΔSI) are never significant (95% CI includes the null hypothesis value 0, $p>0.05$), except one 6-h block. These differences are never significant when using Bonferroni correction ($p>0.004$). Additionally, these differences are always within the equivalence range (Fig. 2). Males and females thus have equivalent metabolic variability and should be equally easy or hard to control.

4. DISCUSSION

The results presented suggest two main outcomes. One based on SI significant difference between genders, and the second on equivalent variability. Specifically, females are more insulin resistant and have a stronger metabolic response to stress, and males and females are equally hard to control.

In this retrospective cohort, male and female sub-groups demographics and GC outcomes are similar (Table 1). The only significant differences are in the overall median cohort BG distribution and nutrition rates achieved. However, the difference in BG levels is well within clinical equivalence (Uyttendaele*, et al.*, 2017), and the significant difference in nutrition rates achieved (g/h) is explained by the difference in the original goal feed (GF). When comparing nutrition rates in terms of %GF achieved, which is based on body size, the difference, as expected, disappears and %GF rates are similar. Thus, both groups are demographically similar.

Weight information is not available for SPRINT patients. However, GF is calculated starting from the 2000kcal/day recommended by ACCP guidelines, and then adapted for each patient based on sex, age, and body frame size. GF thus ranges from ~1025 – 2450 kcal/day. Frame size approximates body mass into three groups, while age captures change in energy demands as age increases. Thus, these metrics account for body mass and demand to personalise nutrition goals.

GF (g/h) is higher for males (Table 1), as they typically have higher body mass, so this difference is expected. However, %GF is the same between the sexes, and thus overall caloric goals per body mass and estimated demand by age are similar across both cohorts. Hence, given insulin administration and %GF delivered are the same, it can be concluded females were given similar g/hr of nutrition per body weight and demand, but were given greater insulin per body mass or frame size. Specifically, %GF is normalised to mass in part; but insulin delivery is not. Therefore, females require more insulin per unit of estimated body mass to remove similar amounts of glucose given per unit of estimated body mass.

Therefore, the first main outcome of this study, all else equal, is the significantly lower identified SI observed in females (Table 2), suggesting a stronger metabolic stress response compared to males. Additionally, the similar insulin and grams of dextrose per unit estimated body mass administered during GC, suggest higher insulin dosing per body mass was needed for females, further validating the lower SI levels identified in women. These results match neonatal ICU results (Dickson*, et al.*, 2015a; Dickson*, et al.*, 2015b), where preterm girls had higher insulin secretion at similar glycemia, and thus greater insulin resistance, than boys.

The second main outcome is the equivalent metabolic variability (%ΔSI) between males and females (Fig. 2). The difficulty to safely and effectively control patients is inter- and intra-patient variability (Chase*, et al.*, 2011b). Being equivalent here, suggest males and females are equally controllable, and thus should all benefit from safe and effective GC. In this SPRINT cohort, GC outcomes achieved were safe, effective, and achieved in a similar manner (Table 1), supporting this result.

Overall, the different SI levels and equivalent SI variability suggest GC protocol design lacking patient-specificity would fail to provide personalised control. Specifically, these results females may require higher insulin dosing for equal GC efficacy, at equal safety. Model-based GC approaches are thus needed to capture both inter- and intra- patient variability, and account for demographic differences between patients.

In this study, patient-specific, model-based SI is identified from a validated physiological model (Docherty*, et al.*, 2012; Lin*, et al.*, 2011). This model has been widely shown to correlate well with gold standards measures (Lotz *et al.*, 2006; McAuley *et al.*, 2011), but is limited by estimates of some parameters. The differences seen in resulting SI, all else equal, could be explained by two parameters: higher endogenous glucose production for females and/or lower insulin secretion.

At equal severity (Table 1), higher than estimated endogenous glucose production, due to metabolic stress and inflammatory response to injury, would suggest higher stress response to injury for females. If insulin secretion is lower for females than estimated here, it would suggest a greater suppression of insulin secretion by stress hormones than for males. A combination of both is most likely, given the impact of stress response on these two parameters (Dungan *et al.*, 2009; McCowen*, et al.*, 2001; Preiser *et al.*, 2014).

The quality of the clinical data from this study is high (Chase *et al.*, 2008a; Chase*, et al.*, 2008b). Identified SI is thus believed highly reflective of metabolic condition, although the identification of this parameter using a model can suffer from inaccuracies. However, the model used has been widely validated in clinical use (Dickson *et al.*, 2013; Penning *et al.*, 2012; Stewart*, et al.*, 2016), and shown high performance in the clinical ranges observed here, minimizing such potential inaccuracies.

The authors did not find any analyses comparing endogenous glucose production and insulin secretion between sexes in critically ill adults. However, due to their acute condition, these parameters could differ in many ways. Such analyses would allow comparison of this study results, first to suggest women could be more resistant to insulin than men, potentially due to a greater response to insult induced stress.

The clinical impact of these results could be limited due to the retrospective data used here. However, this cohort is representative of a large generalised ICU cohort of patients from many years of GC practice.

5. CONCLUSIONS

This study shows a significant difference in SI levels between males and females exists for ICU adults under insulin therapy. Females are more insulin resistant, and this could be due to a higher metabolic response to stress.

Metabolic variability, %ΔSI, is equivalent between males and females. Both groups are thus equally controllable and should benefit from similar GC outcomes. In turn, insulin requirements for females are likely higher, but equal safety and efficacy should be achieved for both groups in GC. These results also potentially add a new dimension for future personalized medicine, and support the use of dynamic, model-based, personalised GC protocol designs.

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