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Association between the preoperative fasting and postprandial C-peptide AUC with resolution of type 2 diabetes 6 months following bariatric surgery

Akhila Mallipedhi[1, 2], Thinzar Min[1, 2], Sarah L Prior[1], Claire MacIver[2], Steve D Luzio[1], Gareth Dunseath[1], Richard M Bracken[1], Saiful Islam[3], Jonathan D Barry[4], Scott Caplin[4], Jeffrey W Stephens[1, 2, 4].

[1]Diabetes Research Group, Institute of Life Sciences, Swansea University, Swansea SA2 8PP, UK.

[2]Department of Diabetes & Endocrinology, Morriston Hospital ABM University Health Board, Swansea SA6 6NL, UK.

[3]Swansea Trial Unit, College of Medicine, Institute of Life Sciences 2, Swansea University, Swansea SA2 8PP, UK.

[4]Welsh Institute of Metabolic and Obesity Surgery, Morriston Hospital ABM University Health Board, Swansea SA6 6NL, UK.

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Correspondence and reprint requests to:

Dr.A.Mallipedhi

Diabetes Research Group, Institute of Life Sciences, Swansea University, Swansea SA2 8PP, UK.Tel: +44 (0)1792 704078; Fax: +44 (0)1792 703214. E-mail: mallipedhi@doctors.org.uk

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Abstract

Background and Aims: Bariatric surgery results in the remission of type 2 diabetes mellitus (T2DM) in morbidly obese subjects. The aim of the study was to investigate the predictive value of both static and dynamic measures of C-peptide in relation to T2DM resolution 6 months after bariatric surgery regardless of the operation type.

Methods and Results: A non-randomized prospective study of 24 participants with T2DM undergoing bariatric surgery. Measurements of fasting and 2-hour plasma glucose, insulin, C-peptide and measures of insulin sensitivity were recorded temporally during an oral glucose tolerance test pre-operatively and 6 months post-operatively. A responder was defined with a fasting glucose <5.6mmol/L and HBA_{1c} <6.0% postoperatively. Within the sample there were 11 responders and 13 non-responders at 6 months. There was a significant difference in the duration of diabetes between the groups. Fasting C-peptide ($P \leq 0.05$) and 2-hour C-peptide ($P \leq 0.05$) were higher in responders compared to non-responders. Significantly higher C-peptide levels were observed preoperatively at all time points for responders, with significantly higher area under the curve (AUC_{0-60} and AUC_{0-120}). Using the lower quartiles for C-peptide levels, both fasting C-peptide (>2.5ng/mL [0.83nmol/L]) and 2-hour C-peptide (>5.2ng/mL [1.73nmol/L]) had a sensitivity and negative predictive value of 100% to predict T2DM remission. Logistic regression showed C-peptide, duration of diabetes and BMI were associated with response. The area under the ROC curve was 0.94 and a regression model predicted diabetes remission with a sensitivity of 85.7% and a specificity of 88.9%.

Conclusions: This study demonstrated that static (fasting) and dynamic (AUC, 2-hour) C-peptide measurements predict T2DM resolution 6 months following bariatric surgery. This work provides insight into C-peptide dynamics as a predictor of response to bariatric surgery.

Keywords: Type 2 diabetes, C-peptide, Insulin, Bariatric surgery, Area under Curve

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Abbreviations

T2DM -Type 2 diabetes mellitus

%EWL -Percentage of excess weight loss

HbA_{1c} -Glycated haemoglobin

OGTT-Oral glucose tolerance test-

GLP-1-Glucagon-like peptide-1

IFG-Impaired fasting glycaemia

IGT-Impaired glucose tolerance

BMI-Body mass index

BPD-Bilio-pancreatic diversion

LSG-Laparoscopic sleeve gastrectomy

LAGB-Laparoscopic adjustable gastric band

RYGB-Roux-en-Y gastric bypass

LDL-C-Low density lipoprotein-cholesterol

HDL-C-High density lipoprotein-cholesterol

HOMA-Homeostasis Model Assessment

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1.1 Introduction

Bariatric or metabolic surgery has been recommended as an effective treatment option for type 2 diabetes mellitus (T2DM) associated with obesity and suboptimal glycaemic control despite lifestyle change [1]. While most patients exhibit a significant improvement in T2DM following surgery, remission of T2DM is not universal with a proportion of patients showing no significant improvement in glycaemic control or recurrence of T2DM at a later stage [2-4] . To date, a definitive clinical and biochemical factor which predicts the resolution of T2DM following bariatric surgery has not been identified [5]. Both Pories and Schauer suggested that T2DM was more likely to remain postoperatively if the duration of T2DM was greater than 5-8 years [6, 7]. It has also been observed that the rate of T2DM remission may be related to the percentage of excess weight loss (%EWL) achieved post-operatively [7-9] and that the %EWL is predictive of increased insulin sensitivity among subjects with and without T2DM [10, 11]. In addition, subjects with insulin treated T2DM and higher glycated haemoglobin (HbA_{1c}) have a reduced likelihood of resolution [7]. Blackstone et al found that both the absence of insulin therapy preoperatively and a shorter duration of T2DM independently predicted remission [12].

Total plasma insulin concentrations are in part dependent on the body mass of an individual and the degree of insulin resistance within an individual [13]. Since C-peptide is a direct measure of insulin production this may provide a more accurate measure of beta-cell insulin responsiveness to glucose [14-16]. An important determinant of T2DM remission is circulating levels of C-peptide that reflects pancreatic beta-cell reserve [17]. In T2DM, insulin levels may be supraphysiological due to a compensatory increase in insulin production associated with insulin resistance. However, in the later stages of T2DM, there is associated beta-cell dysfunction and failure leading to low insulin and C-peptide levels [18, 19]. Higher C-peptide

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levels have been described in subjects with remission of T2DM compared to those without remission [20] suggesting that preoperative C-peptide evaluation may have a role in predicting the best patients for bariatric surgery. This has also been supported by other studies, but the role of C-peptide as a prognostic marker of T2DM remission has not translated to routine clinical practice [20-22]. Most of the studies to date have been conducted in Asian samples, a group who display variation in the T2DM phenotype (e.g. younger onset of diabetes, lower body mass index-BMI) compared to white Caucasian populations. Therefore these studies cannot be generalised. A recent publication reported that a fasting C-peptide level >2.9ng/mL [0.97nmol/L] provides a useful cut off for predicting the resolution of T2DM with a sensitivity of 78% and specificity of 72% in a Chinese sample of subjects [23]. A similar finding was noted in a Dutch study where complete resolution of T2DM was observed in 74% of patients with a preoperative fasting C-peptide levels >3.0 ng/mL (1.0 nmol/L). In contrast, none of the T2DM patients with preoperative fasting C-peptide <3.0 ng/mL (1.0 nmol/L) showed resolution [24].

Our aim was to perform a focussed detailed study to investigate the predictive value of static (fasting) and dynamic C-peptide (2-hour, area under the curve-AUC) measurements during an oral glucose tolerance test (OGTT) in relation to resolution of T2DM 6 months after bariatric surgery regardless of operation type. From the outset our aim was not to examine different surgical techniques on the predictive use of C-peptide, but rather preoperative C-peptide dynamics in relation to the resolution of T2DM.

1.2 Methods

1.2.1 Study participants

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Approval for the study was obtained from the Local Research Ethics Committee (South West Wales; LREC reference 06/WMW02/7). Participants were identified and recruited from patients undergoing a planned bariatric surgical procedure. Entry criteria at the outset included: - both genders, age 20-65 years, body mass index (BMI) >40kg/m^2 and physically fit for surgery. All subjects either had previously diagnosed T2DM, or T2DM diagnosed during an oral 75g OGTT 1 month prior to surgery according to ADA criteria at that time [25, 26]. Participants with pre-existing diabetes treated with diet, oral agents, Glucagon-like peptide-1 (GLP-1) analogues or insulin were included. Participants with impaired glucose regulation comprising of either impaired fasting glycaemia [IFG] (5.6-6.9mmol/L) or impaired glucose tolerance [IGT] (2-hour glucose: 7.8-11.0mmol/L) [25] were excluded.

1.2.2 Study design

Participants were recruited prospectively and consecutively from the Bariatric Surgical clinic and were not blindly allocated to a surgical treatment option. As per local guidance at the time of recruitment, those with a BMI>50kg/m^2 were routinely offered bilio-pancreatic diversion (BPD), whereas those with a BMI below this were usually offered laparoscopic sleeve gastrectomy (LSG). LSG was a standard sleeve i.e. sleeve fashioned around a 32F bougie taken from 5cm proximal to the pylorus and up to the left crus. BPD involved a distal gastrectomy (as described by Scopinaro [27]) and a 50cm common channel. A smaller proportion of participants had undergone laparoscopic adjustable gastric band (LAGB) and a Roux-en-Y gastric bypass (RYGB). LAGB was performed using the Pars Flaccida technique and RYGB by creating a small stomach pouch starting below the second major vessel on the lesser curve and 100/100cm alimentary and biliopancreatic limbs. All participants were recruited pre-operatively and seen post-operatively at 6 months where they underwent a standardized 75g OGTT (122mls of Polycal 61.9g/100ml of glucose, Nutricia Clinical Care,

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Trowbridge, UK). Previous studies have demonstrated that the level of glycaemia reached 2 hours after 75g of glucose is closely related to the level of glycaemia after a standardized meal indicating an OGTT is a valid tool for revealing altered carbohydrate metabolism during a meal [28]. Insulin or oral hypoglycemic agents were omitted the night before the OGTT. There was no standardized meal prescribed for the night before and subjects were asked to fast from the midnight before the test.

1.2.3 Baseline clinical and biochemical information

Baseline clinical measurements consisted of weight, height, body mass index (BMI), waist circumference, systolic and diastolic blood pressure. Baseline biochemical measurements (total cholesterol, low density lipoprotein-cholesterol [LDL-C], high density lipoprotein-cholesterol [HDL-C] and triglycerides) were analyzed within the local hospital accredited laboratory. Glucose (Roche Modular P800 Analyzer) and insulin and C-peptide (Roche E170 Modular Analyzer) were also measured locally. During the OGTT, plasma and serum samples were collected for measurements of glucose, insulin and C-peptide at time 0, 15, 30, 45, 60 and 120 minutes. All samples were collected on ice, centrifuged and separated within one hour of collection and subsequently stored at -80^{o}C until analysis.

1.2.4 Measurements of insulin sensitivity

The Homeostasis Model Assessment (HOMA) was used to estimate steady state beta cell function (%B) and insulin sensitivity (%S) preoperatively and postoperatively were calculated using the Oxford University on-line calculator (http://www.dtu.ox.ac.uk/homacalculator, accessed 7th May 2013) [29]. HOMA-IR is the reciprocal of HOMA %S. HOMA %S represent values of 100% in normal young adults when using currently available assays for insulin, specific insulin or C-peptide. The accuracy of

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these measures has been validated and has been shown to correlate with clamp-derived indices of insulin sensitivity and secretion [30]. The fasting C-peptide to insulin ratio was calculated as an index of hepatic insulin clearance [31].

1.2.5 Statistical analysis

A responder at 6 months was defined as a subject with a fasting plasma glucose <5.6mmol/L and HbA_{1c} <6.0% at 6 months. This is in line with established criteria for evaluating the resolution of diabetes 12 months after bariatric surgery based on fasting glucose and HbA_{1c} [32]. A non-responder was defined as a subject not achieving these criteria.

Statistical analysis was performed using SPSS (version 22, SPSS Inc., Chicago). Results for continuous variables are presented as mean and standard deviation and in graphical representation as mean and standard error. Triglyceride did not have a normal distribution and underwent log transformation to normalize the data for analysis and is described with the geometric mean and approximate standard deviation. Mean differences between responders and non-responders were examined using an independent sample t-test for continuous variables and by a Chi-squared test for categorical variables. For insulin and C-peptide, the mean values at the time points of the OGTT were compared to the time at 0 minutes using a paired t-test. Changes in the area under the curve over 30 (AUC_{0-30}), 60 (AUC_{0-60}) and 120 minutes (AUC_{0-120}) were analyzed during the OGTT preoperatively and 6 months postoperatively for glucose, insulin and C-peptide using the trapezoidal rule. In all cases a $P \leq 0.05$ was considered statistically significant. Correlations were examined using Pearson's correlation. Sensitivity, specificity, positive and negative predictive values were calculated for the median and lower quartile cut-off values of fasting and 2-hour C-peptide as predictors of diabetes remission.

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We used a logistic regression model to ascertain the effects of preoperative fasting C-peptide, BMI and duration of the diabetes in relation to diabetes outcome 6 months postoperatively. This is in line with a previous study by Dixon et al [23]. Diabetes outcome (responder vs non-responder) was considered as the response variable and fasting C-peptide, BMI and duration of the diabetes as the predictors in the binary logistic regression model. We did not include the 2-hour C-peptide measurement since it was highly correlated with the fasting C-peptide and thus would increase the possibility of multicolinearity which would thereby violate the regression model's assumption. We also calculated sensitivity and specificity and the receiver operator characteristic (ROC) curve to check the predictive power of the regression model for predicting diabetes remission 6 months following surgery.

1.3 Results

1.3.1 Participant characteristics

The sample comprised of 24 white Caucasian subjects with T2DM with a mean age of 49.2 ±6.2 years (range 38-62 years). In line with previous publications, there were significant reductions 6 months postoperatively compared to baseline for BMI (55.7 ±12.0 v 44.0 ±9.9 kg/m^2, P<0.001), weight (158.3 ±38.9 v 124.8 ±31 kg, P<0.001) and waist circumference (145 ±18 v 125 ±19 cm, P<0.001). The mean excess weight loss was 33.5 ±18.9 kg, P<0.001 with a mean %EWL of 59.7 ±18.0%. Significant improvements were also observed in 2-hour plasma glucose (15.4 ±4.3 v 9.1 ±5.5 mmol/L, p<0.001) and HbA_{1c} (7.6 ±1.5 v 6.3 ±1.3%, P=0.01). Fasting plasma glucose was not statistically different at 6 months (9.6 ±4.3 v 6.3 ±2.9 mmol/L, P=0.07). No changes were observed in LDL-C, HDL-C and systolic blood pressure postoperatively. There was a significant reduction in diastolic blood pressure (79 ±9 v 73 ±12 mmHg, P=0.02).

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1.3.2 Responder and non responders

1.3.2.1 Static measures of glucose and insulin homeostasis

Within the sample there were 11 responders and 13 non-responders at 6 months including 16 females and 8 males. Table 1 shows the baseline preoperative measures grouped by responder status at 6 months postoperatively. No differences were observed in body mass, fasting and 2-hour glucose and HbA_{1c} by responder status, however, there was a significant difference ($P<0.05$) in the duration of diabetes between the groups. Fasting C-peptide ($P\leq0.05$) and 2-hour C-peptide ($P\leq0.05$) were also higher in responders compared to non-responders. Of interest the reduction in BMI in the responder compared to the no-responders following surgery was not statistically significant (-13.7 ±5.7 v -10.2 ±6.7 kg/m^2, P=0.19).

1.3.2.2 Dynamic measures of glucose and insulin homeostasis

No differences were observed in the preoperative AUCs for glucose and insulin by responder status. Figure 1 shows C-peptide and insulin values during the preoperative 2-hour OGTT. Significantly higher C-peptide levels were observed preoperatively at all the time points for responders. This is in keeping with significantly higher $AUC_{0\text{-}60}$ and $AUC_{0\text{-}120}$ for C-peptide (Table 2) for responders compared to non-responders.

1.3.2.3 Relationships between C-peptide measurements and duration of diabetes and logistic regression analysis

Fasting C-peptide was correlated with 2-hour C-peptide ($r=0.81$, $P<0.001$) and $AUC_{0\text{-}60}$ ($r=0.95$, $P<0.001$) and $AUC_{0\text{-}120}$ ($r=0.90$, $P=0.001$). In addition 2-hour C-peptide was correlated with $AUC_{0\text{-}60}$ ($r=0.89$, $P<0.001$) and $AUC_{0\text{-}120}$ ($r=0.96$, $P=0.001$). No correlation was observed between duration of diabetes and fasting C-peptide ($r=-0.08$, $P=0.77$), 2-hour C-peptide ($r=-0.24$, $P=0.37$), $AUC_{0\text{-}60}$ ($r=-0.20$, $P=0.45$) and $AUC_{0\text{-}120}$ ($r=-025$, $P=0.35$).

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The results of the logistic regression model showed a good fit to the data according to the Hosmer and Lemeshow goodness of fit test (the Chi-square test statistics is not significant as P>0.05). The model explained 65.5% of the diabetes remission (Nagelkerke R^2) 6 months postoperatively. The overall predictive accuracy was 87.5% according to the classification table of the logistic regression model. However, even though the model was significant, none of the predictors were statistically significant. This is likely to be because of the small size and the existence of missing values. The equation of the regression model was as follows:-

In(odds) = 4.1 – 0.154 (BMI) + 1.4 (fasting C-peptide) – 0.028 (duration of diabetes)

It is evident from the regression equation that both BMI and duration of diabetes have a negative effect on diabetes remission after 6 months (i.e. higher the preoperative BMI and/or duration of diabetes, the less likely to have the remission after the surgery). In contrary, fasting C-peptide was found to have a positive effect and was the biggest predictor (highest odds ratio in the model) of diabetes remission. The area under the ROC curve was 0.94 which suggests that the logistic regression model is robust in differentiating between a responder and non-responder at follow-up. The coordinates of the ROC curve are shown in Figure 2 along with the coordinates table (Table 3). These show that the regression model predicts the remission of diabetes with a sensitivity of 85.7% and a specificity of 88.9%.

1.3.2.4 Preoperative quartiles of static and dynamic C-peptide and diabetes resolution

Figure 3 shows the percentage of responders grouped by quartiles of fasting C-peptide, 2-hour C-peptide and $AUC_{0\text{-}120}$ for C-peptide. No responders were seen in the lowest quartile for all of these measures. A linear association was observed for C-peptide $AUC_{0\text{-}120}$ across groups. Table 4 shows the sensitivity, specificity, positive and negative predictive values for predicting a responder. These are discrete calculations and are displayed taking the lower

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quartile value and the median values for each fasting C-peptide and 2-hour C-peptide. Using the lower quartile cut-off, both fasting C-peptide and 2-hour C-peptide had a sensitivity and negative predictive value of 100%. Using the median values the sensitivity and negative predictive values were approximately 70% and 60% respectively for both measures.

1.4 Discussion

This small but focused study shows that preoperative static and dynamic C-peptide measurements aid in the prediction of T2DM resolution 6 months following bariatric surgery. To our knowledge, no previous studies have examined preoperative AUCs for C-peptide in relation to T2DM resolution postoperatively. This examination of AUC is thus novel and worthy of reporting. We observed that fasting C-peptide was an independent predictor of T2DM resolution at 6 months. Of interest, a previous study by Dixon and colleagues [(23)] within a Chinese sample observed that a fasting C-peptide >2.9ng/mL (0.97nmol/L) provided predictive accuracy in predicting diabetes resolution. Aarts et al also observed similar cut-off level of fasting C-peptide 3ng/ml [>1nmo/L] in predicting T2DM resolution. We observed that no responders had a fasting C-peptide <2.5ng/mL (0.83nmol/L) (our lower quartile). We also observed that the duration of diabetes, static 2-hour C-peptide, $AUC_{0\text{-}60}$ and $AUC_{0\text{-}120}$ were different between responders and non-responders. These observations re-affirm the role of C-peptide as a prognostic marker. Of note, we observed that duration of diabetes was not correlated with any of the C-peptide markers, suggesting that caution may be required if duration of diabetes is to be used as an exclusive prognostic marker of T2DM resolution. Logistic regression showed C-peptide, duration of diabetes and BMI were associated with response. The area under the ROC curve was 0.94 and a regression model predicted diabetes remission with a sensitivity of 85.7% and a specificity of 88.9%. This is in line with the previous study by Dixon et al in a Chinese sample of subjects[(23)].

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Previously, low levels of C-peptide have been of use in identifying patients at risk of diabetes or with insulin deficiency such as type 1 diabetes and latent autoimmune diabetes in adults [33, 34]. Fasting C-peptide is a relatively simple test to perform and may therefore form an easy and accurate measure, which may aid in predicting the resolution of T2DM postoperatively and the need for potential T2DM related treatments postoperatively at 6 months. In addition the measurement of a 2-hour C-peptide also aids as a predictive method. Whilst the measurement of the AUC for C-peptide may not be practical as a routine test, our study shows good correlation between this the static measurements of C-peptide. Within our current study we did not examine the effects of C-peptide as a predictor of T2DM resolution in relation to different bariatric operations. Our aim was to examine the C-peptide measurements as predictors of response in a bariatric sample of subjects. Clearly different bariatric procedures are associated with different outcomes in relation to T2DM, however there is a growing body of evidence suggesting that LSG, BPD and RYGB may have a similar efficacy in the resolution of T2DM [26, 35]. Strengths of the current study include the well-detailed static and dynamic measurements performed within the white-Caucasian sample of subjects with T2DM. The main limitation of our study was the small number of patients included. Further studies are required with subjects from different cultural backgrounds after stratifying by types of surgery, and we would also suggest that such a study re-examines the subjects for longer periods post-operatively (e.g. 12 months and beyond).

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Table and Figure legends

Table 1: Baseline characteristics of participants

LAGB: Laparoscopic adjustable gastric band; LSG: Laparoscopic sleeve gastrectomy; BPD: Biliopancreatic diversion; RYGB: Laparoscopic Roux-en-Y Gastric Bypass.

*Geometric mean and approximate standard deviation shown for log-transformed data.

Table 2: Preoperative AUCs for glucose, insulin and C-peptide in responders and non responders at 6 months

AUC: Area under the curve for 0-30, 0-60 and 0-120 minutes.

Table 3: Coordinates of the ROC Curve from logistic regression

*The smallest cut-off value is the minimum observed test value minus 1, and the largest cut-off value is the maximum observed test value plus 1. All the other cut-off values are the averages of two consecutive ordered observed test values. We observed from the results of the coordinates table that the regression model predicts the remission of diabetics with a sensitivity of 85.7% and a specificity of 88.9%.

Table 4: Sensitivity, specificity, positive and negative predictive values of C-peptide measurements for resolution of T2DM

*Median value; †Lower quartile cut off.

PPV: Positive predictive value; NPV: Negative predictive value.

95% confidence intervals shown.

*Median value; †Lower quartile cut off.

PPV: Positive predictive value; NPV: Negative predictive value.

95% confidence intervals shown.

Figure 1: ROC curve using BMI, duration of diabetes and fasting C-peptide for predicting diabetes remission 6 months following surgery

The area under the ROC curve is 0.94.

Figure 2: C-peptide and insulin measurements during the 2 hour oral glucose tolerance test preoperatively in relation to responders and non responders at 6 months

Mean and standard error is shown. *$P \leq 0.05$.

Figure 2a: C-peptide. Significant differences in C-peptide were observed at all time points apart from 15 minutes between responders and non-responders at 6 months.

Figure 2b: Insulin. No differences were seen with respect to insulin at any time points between responders and no responders.

Figure 3: Percentage of responders grouped by preoperative quartiles of fasting C-peptide, 2-hour C-peptide and $AUC_{0\text{-}120}$ for C-peptide

Figure 3a: Fasting C-peptide. No responders were observed to be in the lowest quartile of fasting C-peptide (≤2.5ng/mL). Chi-squared analysis of the differences between the four groups revealed a significant difference (P=0.03).

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Figure 3b: 2-hour C-peptide. No responders were observed to be in the lowest quartile of 2-hour C-peptide (≤5.2ng/mL). Chi-squared analysis of the differences between the four groups revealed was not significant (P=0.07).

Figure 3c: $AUC_{0\text{-}120}$. No responders were observed to be in the lowest quartile of 2-hour C-peptide (≤7.7281 ng h mL^{-1}). Chi-squared analysis of the differences between the four groups revealed was not significant (P=0.07), but a significant linear association was observed across groups (P=0.03).

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References

1. Dixon JB, Zimmet P, Alberti KG, Rubino F. Bariatric surgery: an IDF statement for obese Type 2 diabetes. Arq Bras Endocrinol Metabol. 2011;55(6):367-82.
2. Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med. 2004;351(26):2683-93.
3. DiGiorgi M, Rosen DJ, Choi JJ, Milone L, Schrope B, Olivero-Rivera L, et al. Re-emergence of diabetes after gastric bypass in patients with mid- to long-term follow-up. Surg Obes Relat Dis. 2010;6(3):249-53.
4. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med. 2009;122(3):248-56 e5.
5. Rubino F, Kaplan LM, Schauer PR, Cummings DE. The Diabetes Surgery Summit consensus conference: recommendations for the evaluation and use of gastrointestinal surgery to treat type 2 diabetes mellitus. Ann Surg. 2010;251(3):399-405.
6. Pories WJ, MacDonald KG, Jr., Morgan EJ, Sinha MK, Dohm GL, Swanson MS, et al. Surgical treatment of obesity and its effect on diabetes: 10-y follow-up. Am J Clin Nutr. 1992;55(2 Suppl):582S-5S.
7. Schauer PR, Burguera B, Ikramuddin S, Cottam D, Gourash W, Hamad G, et al. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. Ann Surg. 2003;238(4):467-84; discussion 84-5.
8. Sugerman HJ, Wolfe LG, Sica DA, Clore JN. Diabetes and hypertension in severe obesity and effects of gastric bypass-induced weight loss. Ann Surg. 2003;237(6):751-6; discussion 7-8.
9. Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA. 2008;299(3):316-23.
10. Dixon JB, Dixon AF, O'Brien PE. Improvements in insulin sensitivity and beta-cell function (HOMA) with weight loss in the severely obese. Homeostatic model assessment. Diabet Med. 2003;20(2):127-34.

11. Ballantyne GH, Wasielewski A, Saunders JK. The surgical treatment of type II diabetes mellitus: changes in HOMA Insulin resistance in the first year following laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic adjustable gastric banding (LAGB). Obes Surg. 2009;19(9):1297-303.
12. Blackstone R, Bunt JC, Cortes MC, Sugerman HJ. Type 2 diabetes after gastric bypass: remission in five models using HbA1c, fasting blood glucose, and medication status. Surg Obes Relat Dis. 2012;8(5):548-55.
13. Carey DG, Jenkins AB, Campbell LV, Freund J, Chisholm DJ. Abdominal fat and insulin resistance in normal and overweight women: Direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. Diabetes. 1996;45(5):633-8.
14. Cohen RV, Pinheiro JC, Schiavon CA, Salles JE, Wajchenberg BL, Cummings DE. Effects of gastric bypass surgery in patients with type 2 diabetes and only mild obesity. Diabetes Care. 2012;35(7):1420-8.
15. Bonser AM, Garcia-Webb P. Acute effects of insulin on surface insulin receptors in isolated hepatocytes. Evidence for a recycling pathway. Biochemical and biophysical research communications. 1984;119(2):706-12.
16. Garcia-Webb P, Zimmet P, Bonser A, King H, Bottomley S. Factors affecting fasting serum C-peptide levels in Micronesians: comparison with a Caucasoid population. Diabetologia. 1984;27(1):23-6.
17. Nannipieri M, Mari A, Anselmino M, Baldi S, Barsotti E, Guarino D, et al. The role of beta-cell function and insulin sensitivity in the remission of type 2 diabetes after gastric bypass surgery. J Clin Endocrinol Metab. 2011;96(9):E1372-9.
18. Landin-Olsson M. Latent autoimmune diabetes in adults. Ann N Y Acad Sci. 2002;958:112-6.
19. Lee WJ, Ser KH, Chong K, Lee YC, Chen SC, Tsou JJ, et al. Laparoscopic sleeve gastrectomy for diabetes treatment in nonmorbidly obese patients: efficacy and change of insulin secretion. Surgery. 2010;147(5):664-9.
20. Lee WJ, Chong K, Ser KH, Chen JC, Lee YC, Chen SC, et al. C-peptide predicts the remission of type 2 diabetes after bariatric surgery. Obes Surg. 2012;22(2):293-8.
21. Lee WJ, Chong K, Chen JC, Ser KH, Lee YC, Tsou JJ, et al. Predictors of diabetes remission after bariatric surgery in Asia. Asian J Surg. 2012;35(2):67-73.
22. Lakdawala M, Shaikh S, Bandukwala S, Remedios C, Shah M, Bhasker AG. Roux-en-Y gastric bypass stands the test of time: 5-year results in low body mass index (30-35 kg/m(2)) Indian patients with type 2 diabetes mellitus. Surg Obes Relat Dis. 2013;9(3):370-8.
23. Dixon JB, Chuang LM, Chong K, Chen SC, Lambert GW, Straznicky NE, et al. Predicting the glycemic response to gastric bypass surgery in patients with type 2 diabetes. Diabetes Care. 2013;36(1):20-6.
24. Aarts EO, Janssen J, Janssen IM, Berends FJ, Telting D, de Boer H. Preoperative fasting plasma C-peptide level may help to predict diabetes outcome after gastric bypass surgery. Obes Surg. 2013;23(7):867-73.
25. Dominguez-Vega G, Pera M, Ramon JM, Puig S, Membrilla E, Sancho J, et al. A comparison of laparoscopic versus open repair for the surgical treatment of perforated peptic ulcers. Cir Esp. 2013.
26. Mallipedhi A, Prior SL, Barry JD, Caplin S, Baxter JN, Stephens JW. Temporal changes in glucose homeostasis and incretin hormone response at 1 and 6 months after laparoscopic sleeve gastrectomy. Surg Obes Relat Dis. 2014.
27. Scopinaro N, Gianetta E, Civalleri D, Bonalumi U, Bachi V. Bilio-pancreatic bypass for obesity: 1. An experimental study in dogs. Br J Surg. 1979;66(9):613-7.

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28. Wolever TM, Chiasson JL, Csima A, Hunt JA, Palmason C, Ross SA, et al. Variation of postprandial plasma glucose, palatability, and symptoms associated with a standardized mixed test meal versus 75 g oral glucose. Diabetes Care. 1998;21(3):336-40.
29. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care. 1998;21(12):2191-2.
30. Uwaifo GI, Fallon EM, Chin J, Elberg J, Parikh SJ, Yanovski JA. Indices of insulin action, disposal, and secretion derived from fasting samples and clamps in normal glucose-tolerant black and white children. Diabetes Care. 2002;25(11):2081-7.
31. Bojsen-Moller KN, Dirksen C, Jorgensen NB, Jacobsen SH, Hansen DL, Worm D, et al. Increased Hepatic Insulin Clearance After Roux-en-Y Gastric Bypass. J Clin Endocrinol Metab. 2013.
32. Buse JB, Caprio S, Cefalu WT, Ceriello A, Del Prato S, Inzucchi SE, et al. How do we define cure of diabetes? Diabetes Care. 2009;32(11):2133-5.
33. Palmer JP. C-peptide in the natural history of type 1 diabetes. Diabetes Metab Res Rev. 2009;25(4):325-8.
34. Bell DS, Ovalle F. The role of C-peptide levels in screening for latent autoimmune diabetes in adults. Am J Ther. 2004;11(4):308-11.
35. Ribaric G, Buchwald JN, McGlennon TW. Diabetes and weight in comparative studies of bariatric surgery vs conventional medical therapy: a systematic review and meta-analysis. Obes Surg. 2014;24(3):437-55.

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Tables

Table 1: Baseline preoperative characteristics of participants

Measurement	Responder (n=11)	Non responder (n=13)	P
Age (years)	47.5 (7.6)	50.7 (6.2)	0.26
Gender (F/M)	8/3	8/5	0.68
Operation (LAGB, LSG, BPD, RYGB)	0/6/4/1	2/3/6/2	0.31
Duration of diabetes (months)	39 (30)	91 (57)	0.03
Weight (kg)	153.7 (44.9)	162.2 (32.5)	0.60
BMI (kg/m^2)	52.6 (10.0)	58.4 (13.3)	0.25
Waist (cm)	142 (23)	151 (19)	0.29
Excess weight (kg)	81.4 (37.6)	92.5 (32.1)	0.45
% Excess weight	50.9 (9.5)	55.6 (8.7)	0.22
Systolic BP (mmHg)	130 (110)	140 (21)	0.16
Diastolic BP (mmHg)	75 (10)	83 (7)	0.03
LDL-C (mmol/L)	2.4 (0.9)	2.0 (0.6)	0.16
HDL-C (mmol/L)	1.1 (0.3)	1.1 (0.3)	0.81
Triglyceride (mmol/L)*	2.8 (1.3)	1.7 (0.4)	0.18
HbA_{1c} (%)	7.8 (1.8)	8.0 (1.3)	0.77
HbA_{1c} (mmol/mol)	62 (19.7)	64 (14.2)	0.77
Fasting glucose (mmol/L)	9.6 (5.0)	9.6 (3.8)	0.97

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2-hour glucose (mmol/L)	14.9 (4.7)	15.9 (4.1)	0.59
Fasting insulin (IU/mL)	31.2 (17.4)	31.2 (14.4)	1.00
2-hr insulin (IU/mL)	116.38 (88.87)	69.91 (71.09)	0.21
Fasting C-peptide (ng/mL)	4.9 (1.9)	3.3 (1.8)	0.05
2-hr C-peptide (ng/mL)	12.1 (6.0)	7.0 (4.9)	0.05
HOMA B	42.2 (27.7)	29.3 (17.2)	0.26
HOMA %S	261.7 (123.6)	256.8 (226.2)	0.96
HOMA- IR	0.438 (0.177)	0.680 (0.505)	0.22
C-pep: Insulin ratio	0.221 (0.075)	0.148 (0.124)	0.15

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Table 2: Preoperative AUCs for glucose, insulin and C-peptide in responders and non responders at 6 months

	Responder	Non responder	P
	AUC_{0-30}		
Glucose (mmol h L^{-1})	5.3 (3.0)	4.5 (1.1)	0.47
Insulin (IU h mL^{-1})	25.5 (15.6)	20.1 (16.0)	0.47
C-peptide (ng h mL^{-1})	3.2 (1.3)	2.0 (1.2)	0.06
	AUC_{0-60}		
Glucose (mmol h L^{-1})	13.0 (5.5)	11.2 (2.9)	0.39
Insulin (IU h mL^{-1})	73.0 (40.7)	50.5 (37.4)	0.23
C-peptide (ng h mL^{-1})	7.8 (3.1)	4.6 (2.7)	0.03
	AUC_{0-120}		
Glucose (mmol h L^{-1})	28.8 (10.3)	25.2 (6.0)	0.38
Insulin (IU h mL^{-1})	186.0 (114.0)	122.8 (87.2)	0.19
C-peptide (ng h mL^{-1})	19.2 (8.2)	10.9 (6.2)	0.02

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Table 3: Coordinates of the ROC Curve from logistic regression

Positive if Greater Than or Equal To*	Sensitivity	1 - Specificity
.0000000	1.000	1.000
.0012721	1.000	.889
.0083456	1.000	.778
.0191814	1.000	.667
.0744818	1.000	.556
.1862974	1.000	.444
.2616588	1.000	.333
.2860215	1.000	.222
.3145491	.857	.222
.4411510	.857	.111
.5503349	.714	.111
.6875347	.571	.111
.8352490	.571	.000
.8850525	.429	.000
.9561757	.286	.000
.9934894	.143	.000
1.0000000	.000	.000

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Table 4: Sensitivity, specificity, positive and negative predictive values of C-peptide measurements for resolution of T2DM

	Sensitivity	Specificity	PPV	NPV
Fasting C-peptide				
>4.25 ng/mL*	67.7% (29.9-92.5%)	63.6% (30.8-89.1%)	64.3% (35.1-87.2%)	100.0% (54.0-100%)
>2.5 ng/mL†	100% (66.4-100%)	54.6% (23.4-83.3%)	100% (54.1-100%)	64.3% (35.2-87.1%)
2-hour C-peptide				
>8.5 ng/mL*	70.0% (34.8-93.3%)	63.4% (30.8-89.1%)	63.6% (30.8-89.1%)	70.0% 34.8-93.3%)
>5.2 ng/mL†	100% (63.1-100%)	45.5% (16.8-76.6%)	42.1% (20.3-66.5%)	100% (47.8-100%)

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Figure 1A

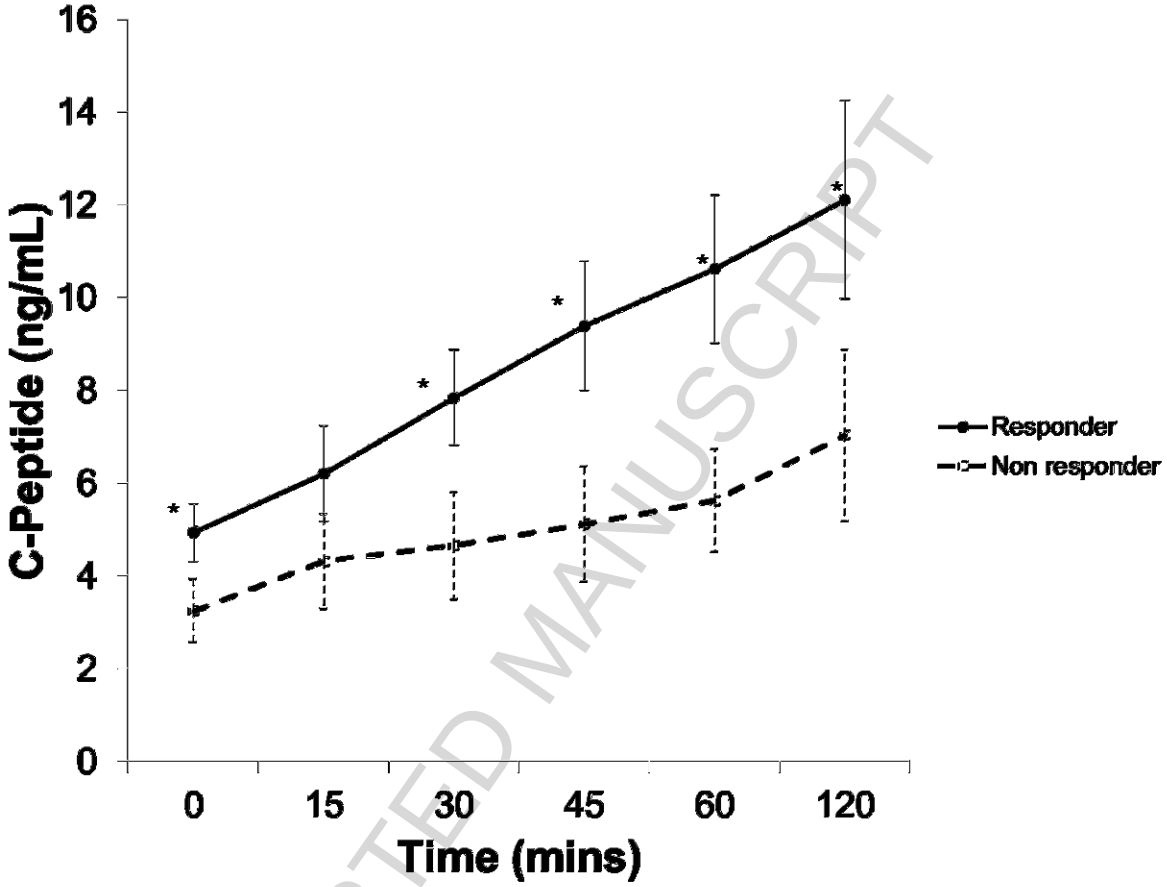

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Figure 1B

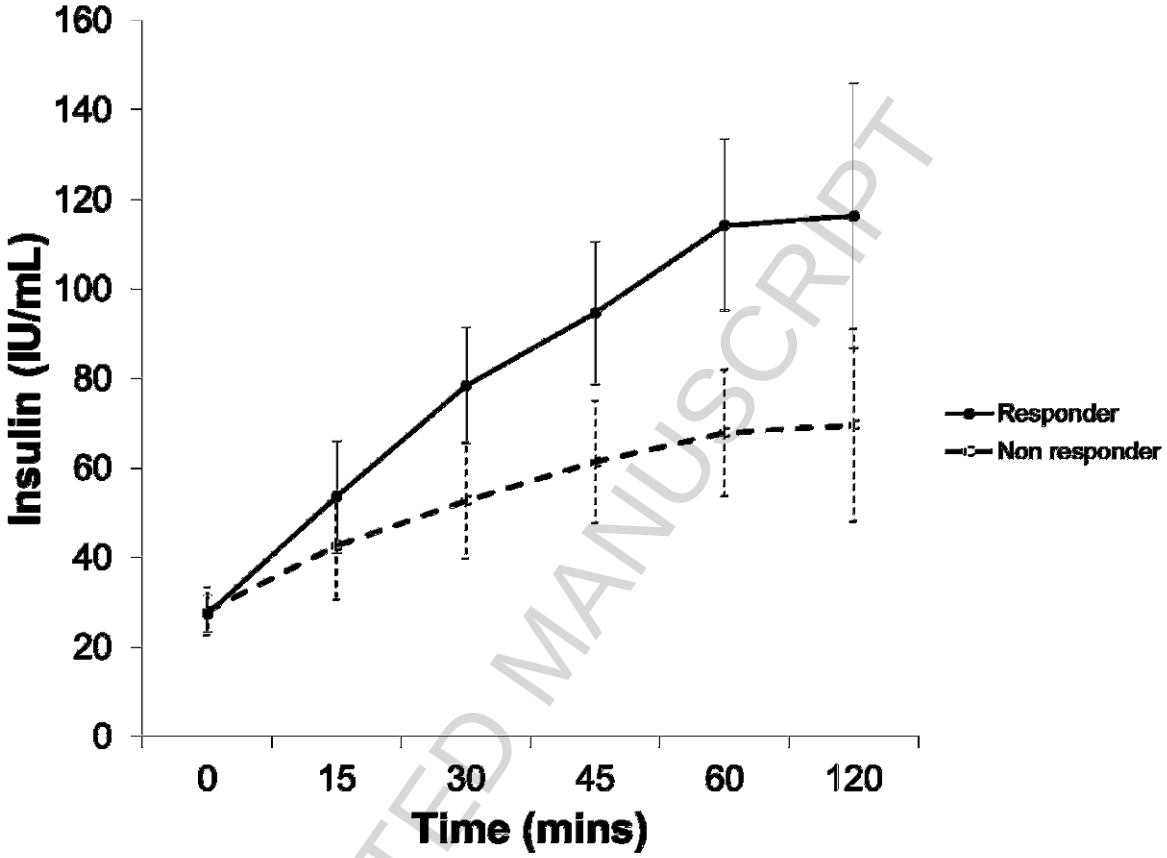

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Figure 2

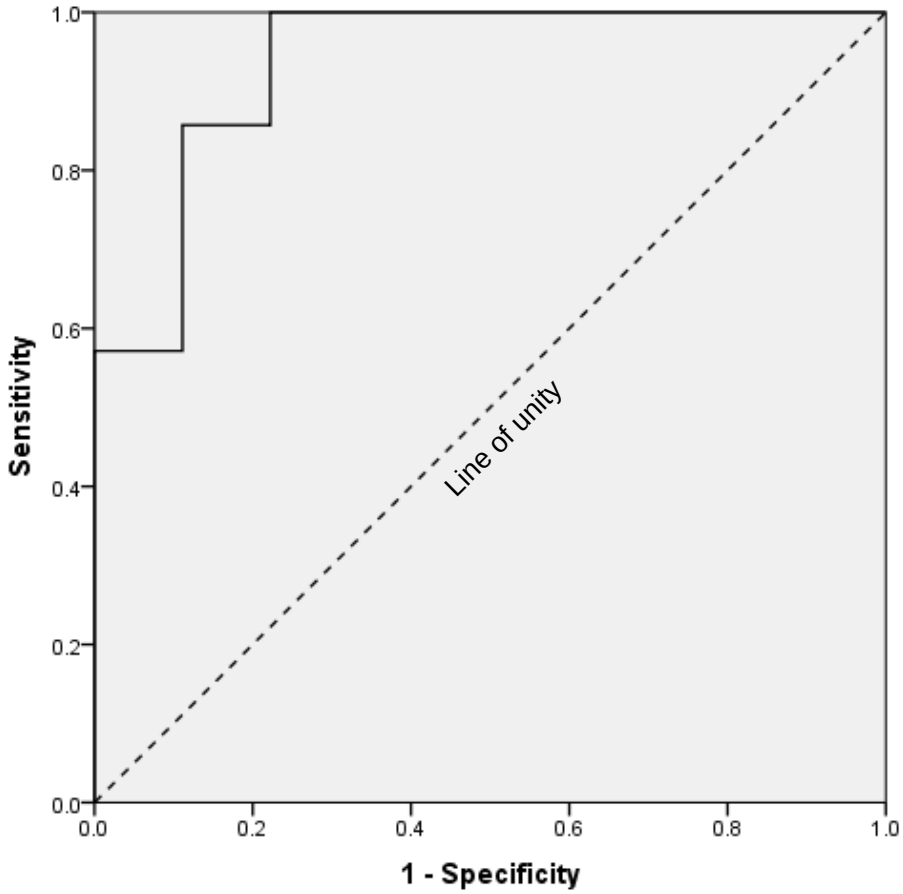

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Figure 3A

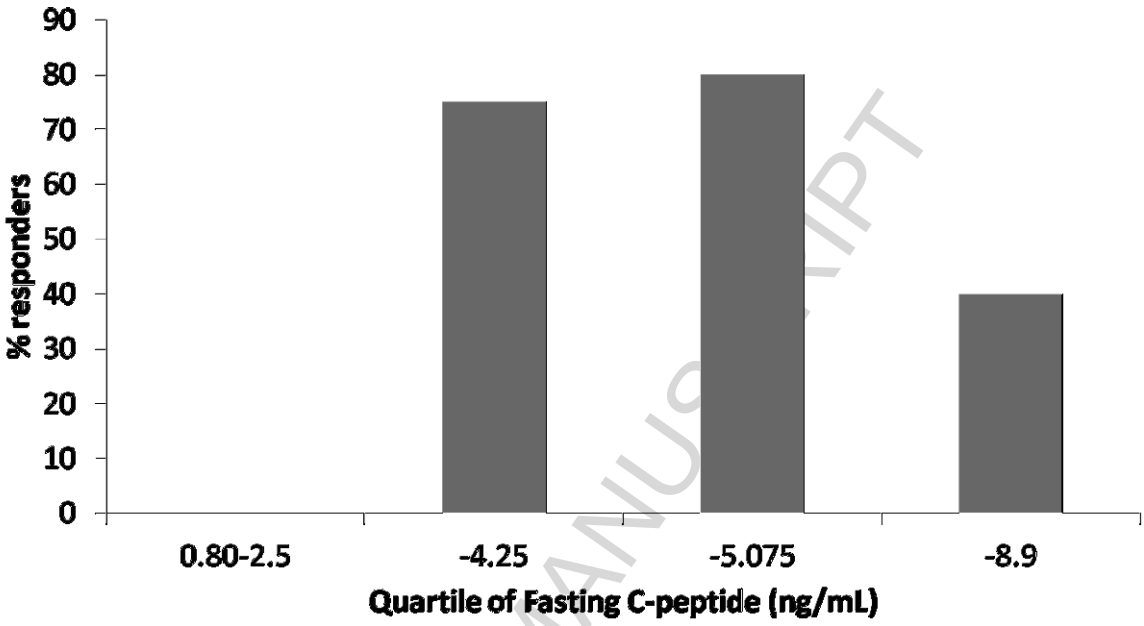

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Figure 3B

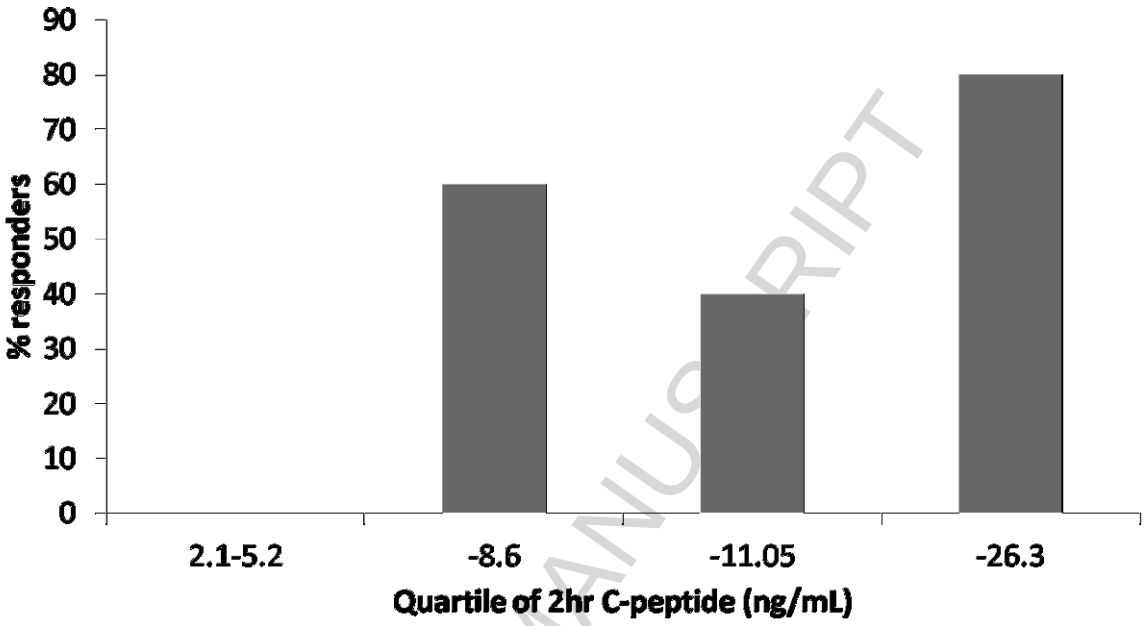

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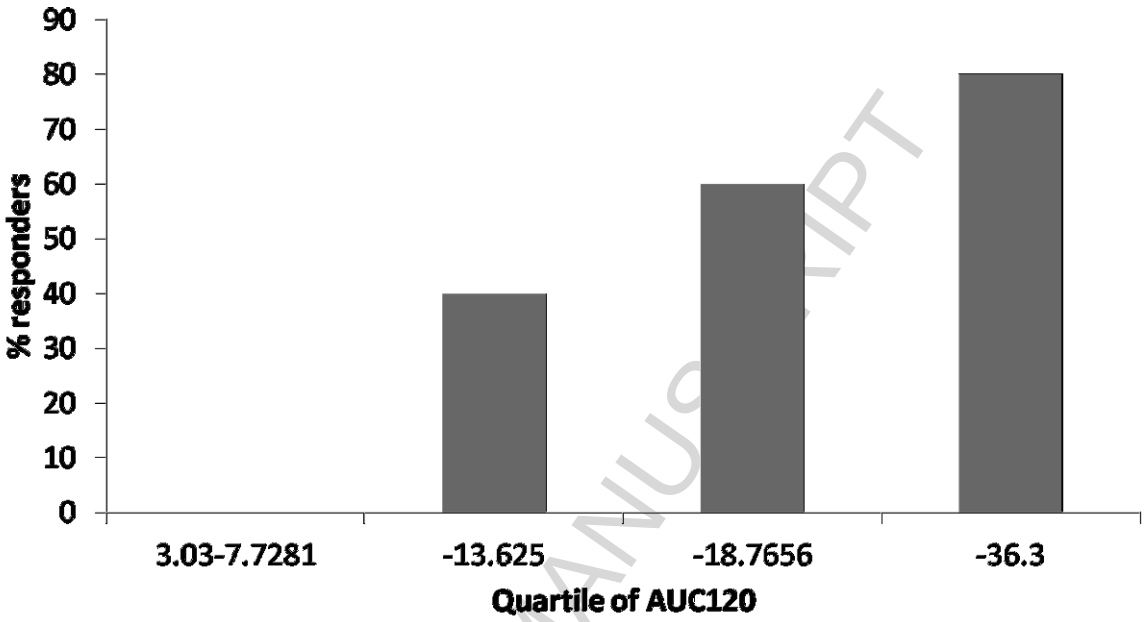
Figure 3C



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