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RESEARCH ARTICLE

Ahmed et al: Hormones and insulin sensitivity

Hormonal predictors of the insulin sensitive phenotype in humans

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ABSTRACT

Clinical obesity, a chronic condition marked by excessive fat accumulation, often leads to insulin resistance and a heightened risk of comorbidities. This study aimed to identify hormonal predictors of an insulin-sensitive phenotype (ISP) in patients undergoing body contouring surgeries, focusing on the relationship between gut hormones, adipokines, and fat mass. ISP was defined as the highest tertile of HOMA insulin sensitivity. We prospectively followed patients undergoing abdominoplasty, lower body lift, or thigh lift at Hamad General Hospital from January 2021 to December 2023. Body composition, glycemic indices, and hormonal levels were assessed, with data analyzed using descriptive statistics and regression models. The study included 34, 22, and 27 subjects at visits 1, 2, and 3, respectively. Fat percentage decreased slightly at visits 2 and 3 compared to baseline, though not significantly. Median levels of glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP), pancreatic polypeptide (PP), liver-expressed antimicrobial peptide 2 (LEAP2), and amylin varied significantly across visits, initially rising at visit 2 before declining at visit 3. Logistic regression revealed that ISP was negatively associated with serum GIP. LEAP2, and leptin levels while positively associated with PP. History of bariatric surgery was only weakly associated with the ISP after hormonal associations were accounted for. Notably, total body fat percentage did not predict ISP after accounting for hormonal factors. This study highlights GIP, PP, leptin, and LEAP2 as key predictors of ISP, with GIP being the primary negative regulator. These findings underscore the importance of hormonal interplay in insulin sensitivity, emphasizing the role of gut hormones and adipokines in predicting ISP in humans.

Keywords: Obesity; adipokines; gut hormones; body contouring surgery; insulin sensitivity; pancreatic polypeptide; PP; gastric inhibitory polypeptide; GIP; leptin; liver-expressed antimicrobial peptide 2; LEAP2.

INTRODUCTION

Clinical obesity is a chronic health condition characterized by the abnormal accumulation of excess body fat, which negatively impacts overall health and significantly increases the risk of various comorbidities. The expansion of adipose tissue is strongly associated with insulin resistance, a metabolic disorder in which the body's cells exhibit reduced responsiveness to normal insulin levels, leading to compensatory hyperinsulinemia. Insulin resistance is a key contributor to numerous comorbidities, including metabolic syndrome, which heightens the risk of cardiovascular diseases and metabolic dysfunction–associated steatotic liver disease [1].

Adipose tissue, in addition to being an efficient energy resource, is considered an endocrine organ that secretes various hormones known as adipokines, which play a major role in maintaining metabolic homeostasis. The accumulation of fat tissue, that leads to insulin resistance, is itself regulated by fat-derived adipokines which are regulated by less well-known mechanisms. In the recent past, key interest has been generated by gut hormones given their association with weight loss in individuals receiving pharmacotherapy with gut hormone analogs. Dysregulation of gut hormones may lead to dysregulation of adipokines and among these adipokines leptin is considered a critical hormone that plays a key role in fat mass regulation [2–4]. It is mainly secreted from adipocytes and its plasma concentration increases in proportion to body fat mass. Circulating leptin crosses the blood-brain barrier to regulate central nervous system functions, particularly in the hypothalamus [5].

Although leptin has clearly been effective in inducing weight loss and insulin sensitivity in leptin deficient individuals, the same has not been found for those with leptin excess in lifestyle related obesity [6]. While leptin excess accrues as fat mass accumulates, the expected effect of leptin on insulin sensitivity, appetite and other expected target effects is not seen. It has been thought that a hormonal co-factor, perhaps also fat derived, and inversely associated with fat mass may be required when obesity is present to avoid leptin resistance [7]. Another hypothesis is that gut hormones may regulate leptin sensitivity with or without such a cofactor and may modulate leptin sensitivity [8]. The latter is indicated by several observations including gut hormones changes post bariatric surgeries and weight loss with gut hormone analogue therapy [9–12].

Body contouring surgery is a group of surgeries where plastic surgeons aim to surgically remove subcutaneous fat tissue, commonly from the abdomen and the thighs, aiming to improve body shape immediately after surgery. These groups of patients represent patients with variable degrees of BMI elevation and/or insulin sensitivity undergoing changes in their subcutaneous fat mass during surgery. Several studies have shown that the metabolic impact of these surgeries may be a decrease in leptin and improvement in insulin sensitivity [7]. However, the underlying mechanisms behind these changes as well as the impact of these surgeries on the incretin and pancreatic hormones have never been reported [13]. Understanding the relationships between body fat, various hormonal changes and insulin sensitivity may provide a better insight to mechanisms linking body fat and the insulin sensitive phenotype (ISP), aiming to provide a better understanding on the mechanisms linking clinical obesity to associated metabolic disease, and differentiate that from preclinical obesity, or what is known as insulin sensitive obese individuals [14].

In the partner paper to this paper , we demonstrate a complex relationship between gut hormones (gastric inhibitory polypeptide (GIP), amylin), leptin and the lean phenotype [15]. In this paper, we look directly at hormonal predictors of insulin sensitivity, to see if the same predictors of the lean phenotype also predict the ISP or if regulation of insulin sensitivity remains distinct from regulation of fat mass.

MATERIALS AND METHODS

Study population

We studied patients who underwent body contouring surgeries at Hamad General Hospital between January 2021 and December 2023, following them at three key time points: preoperatively, and at 2–3 weeks, and 6–10 weeks postoperatively. These time points were selected to capture immediate as well as delayed changes in hormonal profile after surgery.

Eligible participants were adults (≥ 18 years) with a BMI ≥18 who consented to abdominoplasty, lower body lift, or thigh lift. This study included patients with history of bariatric surgery (gastric bypass or sleeve gastrectomy) so long as surgery was done 18 months or more prior to recruitment. These participants were included to facilitate examination of the impact on gut hormones. Exclusion criteria included comorbidities (except non-pharmacologically managed

diabetes), diabetic nephropathy, contouring outside the abdomen or thighs, age > 65, or BMI > 35. Informed consent was obtained from all participants before their inclusion in the study.

Assessment of body composition

The study assessed subjects' body composition before and after surgery using the Tanita (DC-360 P) body composition analyzer, which employs bioelectrical impedance analysis (BIA) technology [16]. This device measures multiple variables, including weight, body fat percentage, body fat mass, BMI, fat-free mass, estimated muscle mass, total body water, visceral fat rating (VFR), and basal metabolic rate (BMR). The Tanita analyzer operates by sending low, safe electrical signals through four metal electrodes; these signals pass quickly through hydrated muscles (water) and encounter resistance when passing through fat tissue. The results are processed using scientifically validated Tanita equations to generate a detailed body composition report [17].

Oral glucose tolerance test (OGTT)

Subjects were required to fast for a minimum of 8 hours prior to the assessment. Fasting glucose levels were first measured in the fasting state. Subsequently, a 75-gram oral glucose drink was administered, and serum glucose levels were measured again at 15, 30, 45, 60, and 120 minutes using a rapid multi-assay analyzer (Analox-GL5).

Glycemic indices

Homeostatic model assessment was made for each subject at the defined time points (before and after the surgery) using the University of Oxford HOMA2 calculator which estimates steady state beta cell function and insulin sensitivity, as percentages of a normal reference population [18]. Samples for c-peptide and fasting glucose were analyzed immediately after collection in the fasted state.

Body contouring surgeries

Subjects who met the inclusion criteria underwent standard surgical procedures, including abdominoplasty, lower body lift, and/or thigh lift. All surgeries were conducted by expert surgeons in the department.

Hormonal measurements

Plasma and serum samples were collected, aliquoted, and stored at -70°C until analysis. Levels of GIP, glucagon-like peptide-1 (GLP-1), Pancreatic Peptide (PP), amylin, and leptin were measured using EMD Millipore’s MILLIPLEX® Human Metabolic Hormone Panel V3, which

utilizes Luminex xMAP technology to simultaneously quantify these analytes in human serum, plasma, tissue lysates, and culture supernatants. Additionally, spexin and Liver Expressed Antimicrobial Peptide 2 (LEAP2) were evaluated using ELISA kits from Abbexa Ltd. All samples were analyzed in duplicate within a single assay to minimize inter-assay variability, and the intra-assay coefficient of variation was maintained below 10% to ensure precision. We only purchased seven hormones (GLP-1, PYY, GIP, amylin, leptin, PP and secretin) out of the possible available within the multiplex system. The latter were chosen as the most relevant hormones of interest and we only reported hormones above which contributed to prediction in the model. Spexin and LEAP2 were separate kits not available within the multiplex system.

Sample size

Sample size calculations were not done because they require knowledge of the true effect in the study, which is always unknown (not only before but also after the study is conducted), and which, if known, would make conducting the study unnecessary [19]. Further, post hoc assessments of power were not done because they are deeply problematic (e.g., they are irrelevant and typically are biased and have large sampling variation) and thus were not calculated [20–23]. Instead, in this paper, we included all participants who were available within the time frame of the study.

Ethical statement

The study received institutional review board approval (IRB) from Hamad medical corporation under reference MRC-01-20-466.

Statistical analysis

Descriptive statistics for patient demographics and variables of interest were reported at each time point (preoperative and postoperative). Differences between these time points were calculated for each variable. Trends in hormonal parameters of interest were evaluated using regression models, with visits (1–3), bariatric surgery status (RYGB, SG, or none), and demographic characteristics included as covariates. Logistic regression models were used to predict the upper tertile of insulin sensitivity which will henceforth be labeled Insulin Sensitive Phenotype (ISP). The correlational structure of repeated measurements in the same patient over time were addressed using cluster robust standard errors. To better understand the relationships, a margins plot was created to depict the results indicated by logistic regression.

To determine if the study data are consistent with a population model that assumes no effect, a *p* value was computed [24]. The exact *p* value is reported and tells us the degree of divergence of the estimated effect from the null hypothesis, had it been the source of the study data. Results in the interval $p < 0.05$ were labeled 'statistically divergent' [24]. To assess clinical benefits, the point estimate and its 95% uncertainty interval (95% UI) for potentially data generating null hypotheses were reported with an assessment of the practical importance of the study result. All analyses were conducted using Stata Version 17 (StataCorp, CollegeStation, TX, USA).

RESULTS

Participants' characteristics

At visits 1, 2, and 3, the number of subjects who attended were 34, 22, and 27, respectively. BMI, fat percentage (Tanita), history of bariatric surgery, and median hormone levels (leptin, spexin, GLP-1, GIP, PP, amylin, and LEAP2) were compared across the three visits (Table 1 Supp.). The gender distribution remained consistent throughout the visits, with females constituting the majority at each time point. BMI values showed minor fluctuations across visits, with no significant differences observed. Fat percentage decreased at visits 2 and 3 compared to baseline, though these changes were not statistically significant. Similarly, the history of bariatric surgery did not show statistically significant variations across the three visits.

Median levels of leptin and spexin fluctuated across visits. Spexin exhibited a consistent upward trend, while leptin levels decreased slightly at visit 2 before rising again at visit 3; however, these changes were not statistically significant. In contrast, GLP-1, GIP, PP, LEAP2, and amylin levels displayed statistically significant variations across visits, with an initial increase at visit 2 followed by a decline at visit 3, indicating notable temporal changes.

Predictors of the ISP

When predictors of ISP were analyzed using logistic regression (Table 1), there was a *negative* association of ISP with serum LEAP2, leptin and GIP levels with the latter demonstrating statistically divergent results. On the other hand, there was a *positive* association of the ISP with PP and history of bariatric surgery, mainly with sleeve gastrectomy, after accounting for the impact of leptin, and gut hormones. A margins plot demonstrated that the probability of ISP was mainly predicted by GIP and the other hormones were modulating this relationship across GIP levels (Figure 1).

An additional analysis was done to include total body fat % (Tanita) within our regression model for predicting ISP and surprisingly was not predictive within the model, after the other hormones in the model were factored in (fat%: OR= 0.965, p = 0.409). This finding is consistent with the observation that increasing fat mass is associated with a pattern of hormonal changes that predict ISP.

DISCUSSION

Our results highlight the complex relationship between LEAP2, PP, leptin, and GIP on the ISP. The findings showed that GIP is a key player in predicting ISP, the probability of which declines as GIP increases. In addition, increases in LEAP2 and leptin were negatively associated with the insulin sensitizing effect of low GIP while PP was positively associated with the insulin sensitizing effect of low GIP. Although our findings show associations, we cannot conclusively determine a cause-and-effect relationship between serum hormone levels and ISP prediction. However, the existing literature presents strong evidence suggesting that these hormones influence the ISP in these individuals.

It is well known that GIP is an incretin hormone and therefore stimulates pancreatic secretion of insulin [25,26]. GIP is associated with insulin resistance, as its levels increase, as shown by our results, and therefore the increase in insulin secretion may also be, at least in part, secondary to increases in insulin resistance. This finding aligns with existing data in the literature, as evidenced by a study conducted on mouse models which showed that administration of GIP receptor antagonist ((Pro^3) GIP) in ob/ob mice led to a significant improvement in insulin sensitivity, independent of any changes in food intake or body weight and that the (Pro^3) GIP-treated group exhibited a significant reduction in pancreatic insulin content and partial amelioration of islet hypertrophy and ß-cell hyperplasia [27]. Another study assessed the effect of high-fat diet on wild-type mice and mice lacking GIP receptors [28]. The wild-type mice developed GIP hypersecretion, extreme visceral and subcutaneous fat deposition, and insulin resistance. In contrast, the mice lacking GIP receptors were protected from obesity and insulin resistance. Furthermore, the effects of (Pro3) GIP injections were investigated in high-fat diet-fed mice over a 160-day period [29]. The results demonstrated that GIP antagonism for 50 days significantly improved insulin sensitivity and facilitated the reversal of glucose intolerance and diabetes. These findings collectively suggest that increasing levels of GIP contribute to insulin

resistance as well as excessive insulin secretion (hyperinsulinemia) and β-cell hyperplasia, making it a promising therapeutic target for improving insulin sensitivity and managing metabolic disorders such as type 2 diabetes.

Our data suggest that PP augments the effect of lower levels of GIP on ISP and thereby should decrease insulin secretion from the pancreas as insulin sensitivity improves with increasing PP levels. This aligns with the body of knowledge in the literature, as PP has been reported to play a role in feeding, body weight and energy balance [30,31]. In a rodent study, PP-sterically stabilized micelles (SSM) improved glucose tolerance and insulin sensitivity in rats with pancreatogenic diabetes caused by pancreatic diseases like chronic pancreatitis and pancreatic neoplasia [32]. Similarly, PP infusion in patients with type 1 or pancreatogenic diabetes on insulin pump therapy enhanced insulin sensitivity and reduced the insulin dose needed to maintain normal glucose levels [33]. A study in obese children found that, at baseline, they had higher insulin resistance, elevated leptin, and lower PP levels compared to normal-weight children [34]. After one year of weight loss, the obese group showed increased PP levels, which correlated with reduced leptin levels and improved insulin sensitivity. Similar findings were found in a study that assessed PP, insulin sensitivity and DPP- IV in obese children over one year of a weight loss intervention program. The results showed significant increase in PP and insulin sensitivity with significant decrease in DPP-IV in children with substantial weight loss [35]. Although we demonstrate that the effect of PP on the ISP opposes that of GIP, several studies have demonstrated that PP also increases as a consequence of increases in GIP. One study investigated the effect of human GIP_{1-42} (hGIP) administration on PP levels. The results revealed that hGIP significantly increases PP secretion in healthy individuals, patients with type 2 diabetes, and isolated porcine pancreata [36]. Additionally, another study examined the impact of hGIP injection on PP secretion in overweight/obese individuals with type 2 diabetes mellitus who were undergoing treatment with metformin and a long-acting GLP-1 receptor agonist [37]. The findings indicated that PP concentrations during GIP infusion were significantly higher compared to those during placebo infusion at all measured time points. The latter results suggest that PP could be responding to GIP receptor activation, the latter inducing a state of insulin resistance, and through unknown mechanisms PP secretion increases to counter this effect. This was not mediated through GLP-1 since it is known that GLP-1 does not stimulate PP secretion [38]. Collectively, these studies underscore the intricate interplay between GIP, PP, and insulin

sensitivity, highlighting the importance of further research to better understand these relationships.

Leptin was associated with an increase in insulin resistance as its levels increased. The leptin effect is paradoxical as it is well known to be an insulin sensitizer, but this finding potentially represents ongoing stimulation of leptin release in a state of leptin resistance [39]. We have reported in our partner paper in this journal that leptin levels go up primarily with fat mass and therefore high leptin is itself a proxy for leptin resistance [15]. This probably explains why high leptin was associated with more insulin resistance in this study. Elevated leptin levels, driven by increased fat mass, are associated with leptin resistance and insulin resistance [15]. This suggests that leptin contributes to impaired insulin sensitivity and lowers the probability of the ISP.

LEAP2 has been shown to be associated with glucose homeostasis and body weight in both human and mouse models. In diet-induced obesity (DIO) mice, LEAP2 levels were significantly higher compared to the control group and were positively correlated with fat mass and body weight [40]. In humans, BMI, body fat percentage, and HOMA-IR showed a positive correlation with LEAP2 levels even after adjusting for age and sex [41]. In another clinical trial that assessed a cohort with prediabetes and overweight/obesity, fasting plasma LEAP2 levels were inversely associated with insulin sensitivity and positively associated with BMI, body weight, and fat mass [42]. The accumulating data therefore indicates that LEAP2, similar to leptin, is negatively associated with insulin sensitivity, aligning with our findings.

The strength of this study lies in a clear analytical plan that is able to correctly model the relationships seen. However, this study is limited by a moderate sample size and therefore may benefit from replication by future researchers. Nevertheless, as indicated in the footnote in table 1, the goodness of fit of the model was quite good despite the moderate sample size.

CONCLUSION

This study demonstrates, for the first time, that GIP, PP, leptin, and LEAP2 are predictors of ISP in humans. A strong negative relationship exists between serum GIP and ISP, which is further modulated by PP, LEAP2, and leptin. It can therefore be concluded that the ISP is modulated by gut hormones which also modulate body fat. This questions the conventional wisdom that body fat is the main regulator of ISP. Figure 2 illustrates these findings and raises key questions for

future research, particularly the mechanisms and pathways underlying this relationship and whether the effects are direct or indirect.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Predictors of ISP using logistic regression.

ISP	OR	P>|z|	95% uncertainty interval
Visit			
1	1 (base)		
2	1.549	0.573	0.339, 7.088
3	0.442	0.211	0.123, 1.591
History of bariatric surgery			
No	1 (base)		
BP	1.483	0.682	0.226, 9.748
SL	2.900	0.754	0.822, 10.226
PP pg/mL	1.005	0.116	0.999, 1.010
GIP pg/mL	0.993	**0.009**	0.987, 0.998
Leptin ug/L	0.944	0.073	0.886, 1.006
LEAP2 pg/mL	0.879	0.221	0.715, 1.081
Constant (baseline odds)	1.968	0.484	0.296, 13.65

*Goodness of fit AUC=0.77; McFaddens R^2 = 0.182; goodness of link ascertained via linktest in Stata
The model was adjusted for time as some samples were taken 15 minutes after glucose load as well as body fat%. However, body fat% was not predictive (OR= 0.965, *p*= 0.409) and was removed from the final model. The 15-minute time points refer only to gut hormones where some samples did not have time 0 available. All HOMA calculations were from fasting samples only (see methods).

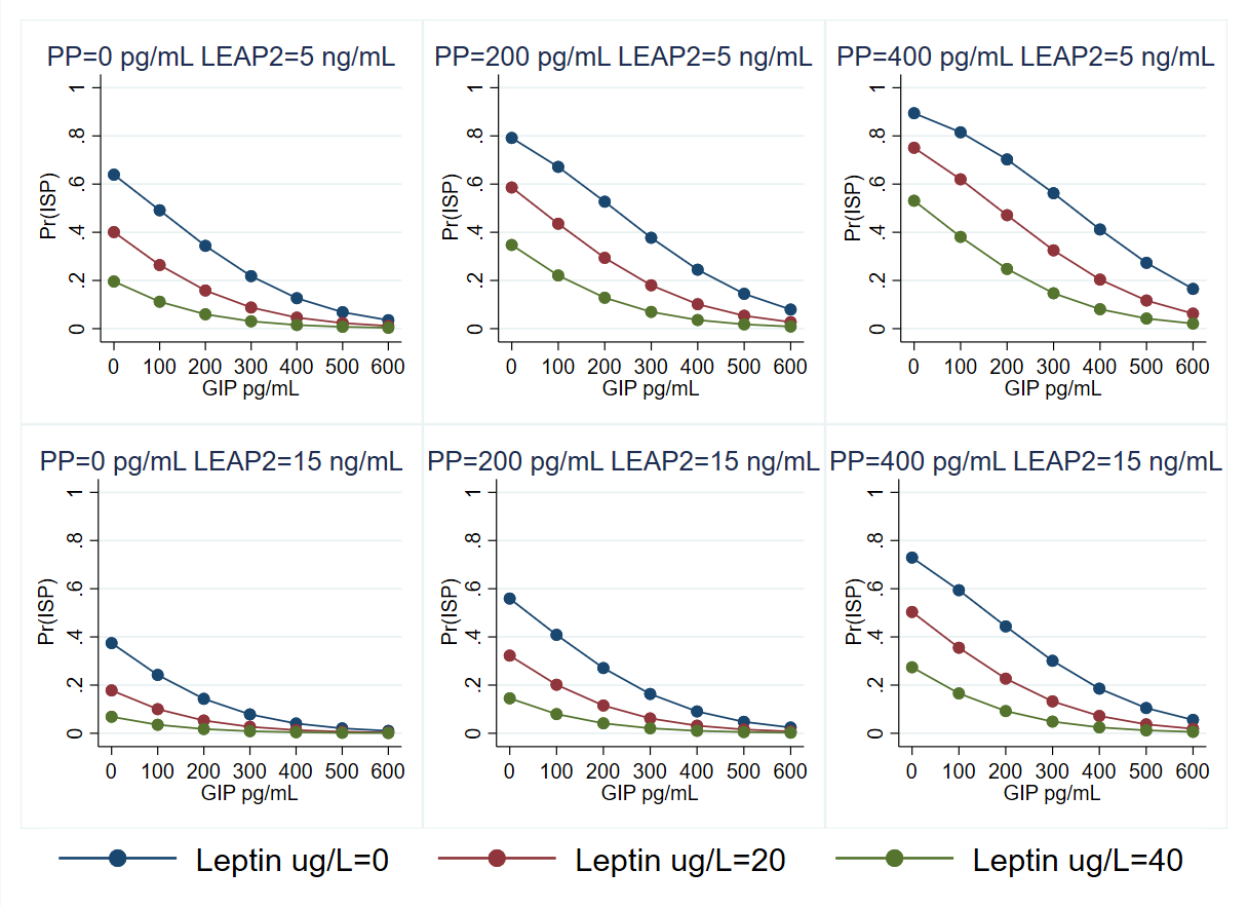

Figure 1. Margins plot with the probability of having ISP as a function of GIP level across three serum leptin (µg/L) levels, two LEAP2 (ng/ml) levels (5 and 15) and three PP (pg/ml) levels (0, 200, 400). These plots derive from the logistic regression model shown in Table 1.

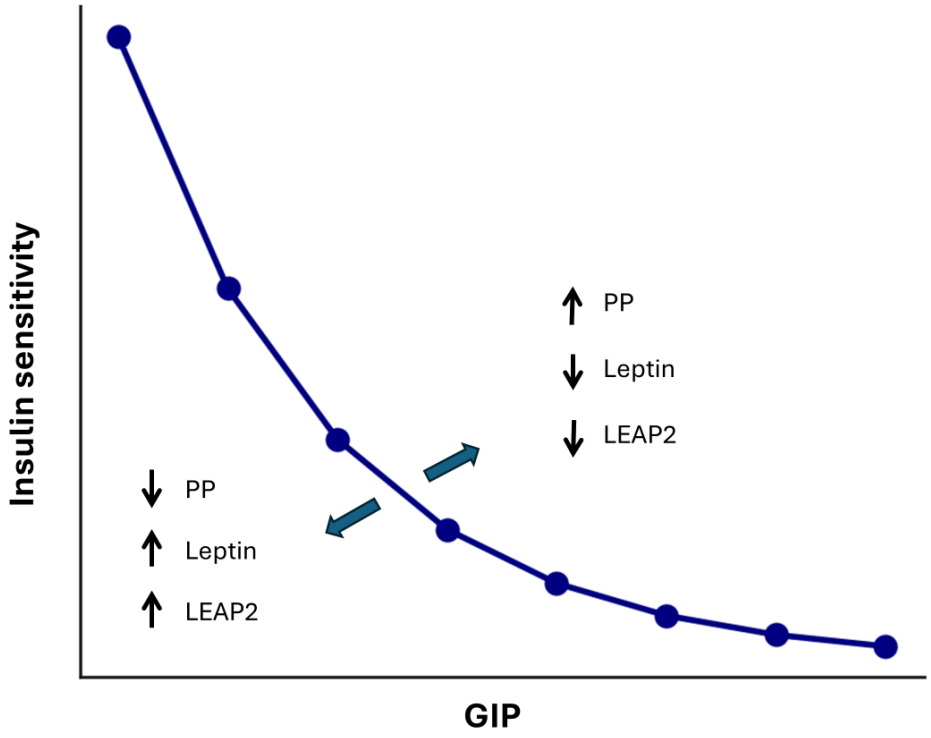

Figure 2. This diagram illustrates the relationship between GIP levels and insulin sensitivity, highlighting key factors that modulate this relationship based on our findings.