Effect of Oral Glucose Loading on Serum Gastrin Level in Pregnant and Non-pregnant Women

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Aim. To evaluate the relationship between the changes in gastrin and insulin serum concentrations after oral glucose loading in pregnant and non-pregnant women.

Methods. Thirty women, 12 pregnant and 18 non-pregnant, with normal fasting glucose values were included in the study. Serum concentrations of gastrin, glucose, insulin, and glucagon were analyzed at 0 (t1), 30 (t2) and 60 (t3) minutes after 75 g oral glucose loading. Gastrin, insulin, and glucagon levels were determined by means of radioimmunoassay kits.

Results. Serum gastrin concentration in pregnant women increased insignificantly (gastrin median values 57.91, 70.62, and 68.70 for t1, t2, and t3, respectively; Friedman’s test, p=0.264). In non-pregnant women gastrin levels insignificantly increased from t1 to t2, but reduced significantly from t2 to t3 (gastrin median values 62.91, 86.92, and 62.25 for t1, t2 and t3, respectively; Bonferroni adjusted Wilcoxon test, p=0.002). Unlike in pregnant women, the changes in gastrin release in non-pregnant women were associated with changes in blood glucose concentrations at t2 and t3, which were induced by oral glucose loading. Glucose median values were 7.48 and 6.43 for t2 and t3, respectively. The insulin release due to the oral glucose loading markedly increased at t2 and t3 (Friedman’s test, p<0.001), whereas glucagon release decreased irrespective of pregnancy.

Conclusion. Changes in blood glucose concentrations induced by oral glucose loading could influence gastrin release, especially in non-pregnant women. Changes in insulin and glucagon levels induced by oral glucose loading, particularly after 60 minutes, could not be associated with changes in gastrin release.

Key words: administration, oral; blood glucose; glucose; glucagon; gastrin; insulin; pregnancy

Gastrin, the major hormonal factor during the gastric phase of acid secretion, is secreted in response to antral distention and presence of food and partially digested protein products (peptides and polypeptides) in the stomach (1). Any free amino acids present also stimulate gastrin secretion, whereas fats have little effect on gastrin release. Vagal stimulation initiated by smelling, tasting, chewing, and swallowing of food also stimulates gastrin release (1). Some studies demonstrated that hyperglycemia reduces gastrin release previously increased by some stimulators (2). For instance, intravenous administration of amino acids stimulates gastrin release, which is subsequently inhibited by the hyperglycemia induced by intravenous infusion of glucose (2). It has also been reported that meal-stimulated gastrin release significantly decreases during hyperglycemia (3). In healthy subjects, infusion of insulin, with subsequent hypoglycemia, stimulates acid secretion (4,5), whereas infusion of glucose to induce hyperglycemia inhibits basal pentagastrin, sham feeding, and meal-stimulated acid output (6-8). Thus, the gastrin release seems to be directly or indirectly mediated by hormonal, neural, and metabolic changes secondary to hyperglycemia.

Hyperglycemia causes an inhibition of gastrin release and increases insulin secretion (4). However, insulin does not inhibit gastric acid secretion, but stimulates acid output only during hypoglycemia (4). In contrast to the studies of inhibitory effect of hyperglycemia induced by intravenous glucose administration on gastrin release (2,6-8), no studies have been conducted to determine the effect of orally
(4). In contrast to the studies of inhibitory effect of hyperglycemia induced by intravenous glucose administration on gastrin release (2,6-8), no studies have been conducted to determine the effect of orally taken glucose on the gastrin release without inducing hyperglycemia. The aim of this study was to determine serum gastrin, glucose, glucagon, and insulin concentrations after oral administration of 75 g glucose, and to evaluate the changes in and relations between the above parameters. Since pregnancy induces hormonal changes (9-12), serum concentrations of gastrin, glucagon, and insulin were monitored in non-pregnant and pregnant women.

Subjects and Methods

Subjects

The clinical trial was carried out in the Mother and Child Health Center in Konya, Turkey, during May 1998. Over a two-week period, 52 pregnant women, 28 of whom 40 were excluded from the study due to the following reasons: 14 women were in their first trimester of pregnancy, when hormonal changes are not as developed as in late pregnancy (11,12), 2 had fasting glucose levels above 6.66 mmol/L, 2 had glucose levels above 11.1 mmol/L after glucose loading (indicating gestational diabetes), 5 had a history of gastrointestinal system disorders, 1 had undergone gastrointestinal surgery, 1 had diabetes mellitus, 2 were on medication (which could have affected the release of studied hormones), 2 had abortions (excluded because of possible effects of the cause of abortion on study parameters), and 11 refused to volunteer. Eighteen non-pregnant women were chosen from those who visited the Center, on the basis of the following criteria: no gastrointestinal disorders, no previous abdominal surgery or abortion, normal fasting glucose levels, normal blood glucose levels after glucose loading (similar to the criteria applied in choosing pregnant women), and no medications. Median ages of pregnant and non-pregnant women were 28 (range 22-35) and 26 years (range 19-38), respectively. The difference in median age between the two women groups was not significant (Mann Whitney U-test, p=0.21). All pregnant women had a 29-week median (range 16-36) of gestational age.

Measurements

Before glucose loading, all subjects were allowed to perform daily physical activity and were on a 3-day diet containing at least 150 g of carbohydrates. At the end of the third day, initial blood samples were collected from the volunteers, who fasted overnight, to measure concentrations of glucose, gastrin, glucagon, and insulin at 0 time-point (t1). Afterwards, glucose loading was performed by oral administration of a single dose of 75 g glucose dissolved in flavored water. The blood samples were collected for analysis from all volunteers 30 and 60 minutes after glucose intake (30- and 60-min time-points).

Each patient’s blood samples were collected into two vacutainers (one coated with ethylene-diamine tetraacetic acid, after which the serum and plasma were promptly separated from the clot. Glucose, insulin, and gastrin concentrations were measured in serum, and glucagon was determined in plasma. Plasma and serum were stored (6 days at longest) at –20°C until analysis. Radioimmunoassay kits were used in measuring insulin (DPC, Los Angeles, CA, USA), glucagon, and gastrin concentrations (ICN Pharmaceuticals, Orangeburg, NY, USA). Serum glucose concentration was detected by glucose oxidase method (Bayer, Berkeley, CA, USA).

Receptive intraassay and interassay coefficients of variations (CV) were: gastrin, 5.8%; insulin, 6.0% and 8.5%; glucagon, 6.5% and 8.0%; and glucose 2.1% and 3.0%.

Statistics

Since the data obtained in this research did not have normal distribution, we used non-parametric descriptive statistics – median and quartiles, instead of mean±SD. The results are presented in box-plots graphs, which show median (the value that divides the distribution into halves) and the first and third quartiles (the value that divides the lowest 25% of the observations from the highest 75%, and the value that divides the highest 25% of the observations from the lowest 75%, respectively). The Friedman test was used to calculate the differences between concentrations in different time points (0, 30, and 60 min) in both pregnant and non-pregnant groups, and Bonferroni-adjusted Wilcoxon test was used to determine which differences were significant. The differences between non-pregnant and pregnant women for each measurement were analyzed by Mann-Whitney U-test. The significance level was set at p<0.05. Statistical program used was SPSS Version 9.0 for Windows Operating System.

Results

Gastrin concentration increased at 30-min time point and decreased at 60-min time point compared to 0 time point. The changes in serum gastrin concentrations (Fig. 1) in different time points (0, 30, and 60 min) were significant in the group of non-pregnant women (Friedman’s test, p=0.009), but not in the group of pregnant women (Friedman’s test, p=0.264). In particular, the decrease in gastrin release from 30-min to 60-min time point was significant in the group of non-pregnant women (Bonferroni adjusted Wilcoxon test, p=0.002). Gastrin value at 60-min time point was significantly lower in non-pregnant than in pregnant women (Mann Whitney U-test, p=0.034).

Glucagon concentrations in pregnant women differed significantly between measurements (Friedman,
p=0.013), in contrast to non-pregnant women (Fig. 2).

The differences between insulin serum concentrations (Fig. 3) at three different time-points (0, 30, and 60 min) were significant in both non-pregnant and pregnant women (Friedman’s test, p<0.001). The increase in insulin concentrations from 0-min time point to 60-min time point was significant in both groups (Bonferroni-adjusted Wilcoxon test, p<0.001), whereas the increase from 30-time point to 60-min time point insulin concentrations was significant only in pregnant women (Bonferroni-adjusted Wilcoxon test, p=0.002). Insulin concentration at 60-min time point was significantly lower in the group of non-pregnant women (Mann Whitney U-test, p=0.051).

Significant changes in glucose concentrations were observed in both groups of women (Friedman’s test, p<0.001, Fig. 4). The increase in glucose concentrations from 0 to 30-min time point was significant in both groups (Bonferroni-adjusted Wilcoxon test, p<0.001), whereas the decrease in glucose concentrations from 30- to 60-min time point was significant in non-pregnant women (Bonferroni-adjusted Wilcoxon test, p=0.022). Glucose serum concentrations at 0 time point were significantly higher in non-pregnant than in pregnant women (Mann Whitney U-test, p=0.002). No significant correlation was observed between the level of gastrin and other measured parameters (glucose, glucagon, and insulin) in either group of women.

**Discussion**

In this study, the blood glucose levels and corresponding insulin levels at 30-min and 60-min time points were significantly increased by oral glucose loading (especially blood glucose at
Therefore, we did not detect inhibition of gastrin release by increased blood glucose concentration in non-hyperglycemic women (at 30-min time point).

Findings in several studies have suggested that gastrointestinal function is affected by glucose concentration (13-17). During acute hyperglycemia induced by intravenous glucose infusion, gastric acid secretion is reduced in healthy subjects (2,18-21). Lam et al (2) showed that acute hyperglycemia significantly reduced the intravenous amino acid-stimulated acid output and gastric release. They also showed that meal-stimulated gastrin release was significantly reduced during hyperglycemia (22). The mechanisms responsible for the inhibitory effect of hyperglycemia on gastrin release are still not known. Sakaguchi et al (23) suggested that portal glucose concentration higher than 10 mmol/L signaled or modulated gastric acid secretion control by gastrin. But, it was possible that hormonal changes resulting from hyperglycemia modulated gastrointestinal function. The modulatory effect of glucose on gastrin release can be mediated indirectly through hormonal or neural changes secondary to changes in glucose concentration. Previous studies have shown that high concentration of insulin does not inhibit but, on the contrary, stimulates acid secretion during hypoglycemia (5). However, the effect of insulin on gastrin release and acid secretion during normoglycemia or hyperglycemia is not known.

The increased insulin release and reduced glucagon release in this study may have been caused by increased blood glucose concentration due to 75 g oral glucose load. However, increased level of insulin did not cause any hypoglycemia by which gastric acid secretion could be directly stimulated. This is contrary to the previous studies in which intravenous administration of insulin stimulated gastric acid secretion (4,5). Similarly, since the inhibitory effect of glucagon on gastrin release is achieved only during the hyperglycemia induced by glucagon infusion (not by glucose infusion) (24), the effect of reduced serum concentration of glucagon due to increased blood glucose concentration in our study could not be the cause of stimulated gastrin release. This may, therefore, indicate that increased insulin release after ingestion of glucose could not be associated with the observed stimulated gastric release unless the level of insulin release had caused hypoglycemia (4,5). Thus, one can speculate that in our study, unlike in previous research (2,3), the initially increased gastrin release might be due to the oral administration of glucose, suggesting that the level of blood glucose was not sufficiently high to induce hyperglycemia that would inhibit gastric release. Our results confirm those of Sakaguchi et al (23), who showed that gastric acid secretion controlled by gastrin could not be inhibited unless the portal glucose concentration was higher than 10 mmol/L. Therefore, in this case, the subsequent increase in blood glucose concentration (under the hyperglycemic glucose values) by oral glucose loading could be the cause of increased gastric release 30 minutes after oral glucose intake. The increased blood insulin concentration could not stimulate gastric release because insulin could not initiate any increase in gastric levels, unless high insulin concentration had induced hypoglycemia. However, this is only a speculation, since the gastrin release is, in fact, controlled not only by blood glucose concentration, but also by hormonal, metabolic, and neural changes in the organism.

Plasma glucagon and serum insulin concentrations are profoundly influenced by pregnancy, since pregnancy is a state of physiologic insulin resistance compensated by an increase of insulin secretion (9). We found glucose concentration significantly low, and insulin and glucagon concentrations significantly high in pregnant women at 0 time point, compared with non-pregnant women. It has been shown that insulin and glucagon concentrations are high during pregnancy (9,10) and that, in late pregnancy, glucose administration causes a marked increase in peripheral insulin concentrations (11). Insulin release after a glucose load increased more in late pregnancy than in non-pregnant state (12). Increased insulin concentrations and/or greater consumption of glucose may explain lower glucose concentrations in pregnant women at 0 time point (11).

In our study, gastrin concentration was increased after 30 minutes compared to 0 time point in both pregnant and non-pregnant women. In non-pregnant women, the gastrin release after 60 minutes decreased, compared with 30-min time point. This appeared to be associated with a decrease in blood glucose concentration, indicating a possible regulation of gastrin release by blood glucose concentration. However, gastrin release in pregnant women continued to increase and was the highest at 60-min time point, irrespective of the reduction in glucose level at the same time-point. It may also be that the blood glucose level could not affect the gastrin release in pregnant women due to the possible metabolic and hormonal changes brought about by pregnancy.

In conclusion, the results of our study suggest that only in hypoglycemic or hyperglycemic conditions it would be possible to detect the mechanism of inhibition or stimulation of gastrin release by changes in blood glucose and insulin concentrations.

References


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