

# Suppression of Insulin Secretion by Ghrelin and The Deterioration of Glucose Tolerance in Healthy Children

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## Summary:

**Background:** Ghrelin, identified as an endogenous ligand for the growth hormone secretagogue receptor, functions as a somatotrophic and orexigenic signal from the stomach. The secretion of ghrelin increases under conditions of negative energy balance, such as starvation, cachexia, and anorexia nervosa, whereas its expression decreases under conditions of positive energy-balance such as feeding, hyperglycemia, and obesity. In addition to having a powerful effect on the secretion of growth hormone, ghrelin stimulates food intake and transduces signals to hypothalamic regulatory nuclei that control energy homeostasis. Thus, it is interesting to note that the stomach may play an important role in not only digestion but also as a pituitary growth hormone release and central feeding regulation.

**Objective:** The goal of this study was to test the hypothesis that circulating ghrelin suppresses insulin secretion in healthy children.

**Subjects and methods:** Enzyne-Linked immunosorbent assay method was used to assay Ghrelin and Insulin. By taking blood sample from 40 obese children, 11 overweight children and 29 normal weight healthy children their age (5-11) years.

**Results:** the mean concentration of Ghrelin was significantly lower in obese and overweight children than in controls (  $P < 0.000$  ). The mean concentration of Insulin was significantly higher in obese and overweight children than in controls (  $P < 0.007$  ). Negative correlations was obtained between Ghrelin and BMI, also negative correlation between Ghrelin and Insulin was obtained.

**Conclusions:** This study showed that ghrelin reduces insulin secretion and glucose disappearance in healthy children. This findings raise the possibility that endogenous ghrelin has a role in physiologic insulin secretion, and that its antagonist may improve  $\beta$ -cell function.

**Key words:** Ghrelin, IGF1, Insulin, Leptin.

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## Introduction:

Ghrelin has gained considerable attention over the last decade for its unique role in regulating mealtime hunger and lipid metabolism, as well as short and long-term energy homeostasis (1). It is the only known circulating factor that promotes food intake and increases fat mass. Ghrelin is secreted mainly from the stomach and proximal small bowel, and stimulates growth hormone (GH) secretion (2), in addition to its effect on energy balance. In healthy subjects, plasma ghrelin levels rise progressively before meals and fall to a nadir within one hour after eating, with changes in plasma levels during meals varying two to three folds (3). Under pathologic conditions associated with severe malnutrition and weight loss, such as anorexia nervosa (4), cancer, or cardiac cachexia (5), plasma total ghrelin levels are increased up to three folds compared with

healthy individuals. Besides its well known effects on feeding behavior, fat mass, and GH secretion, ghrelin has recently been implicated in the regulation of glucose homeostasis (6).

The growth hormone secretagogues ( GHS ) receptor is expressed in the pituitary gland, the hypothalamus (arcuate and ventromedial nucleus), the hippocampus, the raphe nuclei, and the substantia nigra.(7) In addition, low-level expression has been demonstrated in a wide variety of peripheral tissues, including the gastrointestinal tract, liver, pancreas, heart, lung, kidney, adipose tissue, and even immune cells, suggesting a diverse physiologic roles for ghrelin.(8) The full length active GHS receptor is termed GHS-1a, whereas a truncated, apparently inactive, GHS receptor isoform is termed GHS-1b. (9)

**Aim of Study :** The orexigenic gut hormone ghrelin and its receptor are present in pancreatic islets. Although ghrelin reduces insulin secretion in rodents, its effect on insulin secretion in humans has not been yet established.

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**Subjects and Methods:**

This study was performed on 40 healthy obese children, 11 over weight and 29 normal weight children who were selected from subjects attended the public clinic in Al shaab district and from some primary schools in the region . The age of the children was between 5 -11 years.

The study was carried out with the approval of the medical ethical committee in the ministry of health and the parents for blood sampling. The children were thoroughly examined by a doctor and only healthy children with no apparent evidence of endocrine and central nervous system disorders, hypothalamic

tumors and genetic syndromes were selected and then the following information were recorded.

Name, age, sex, and measuring the weight in Kilogram and the height in centimeter.

**Results:**

The results in Table 1 show high level of Ghrelin in normal weight children, low level in obese and overweight children. The correlation is significant between obese and normal weight children and also between overweight and normal weight children.

**Table (1): Mean, standard deviation , Median level of Ghrelin in healthy obese , over weight and normal children**

Group	Mean	N	Std. Deviation	Median	Obese / Over Wt	Obese / Normal	Over Wt / Normal
Obese	295.9428	40	81.52925	316.0700	-	-	-
Over Wt	308.7273	11	47.04396	316.0700	-	-	-
Normal	420.1652	29	137.55964	396.5700	-	-	-
Mean Difference	-	-	-	-	-12.78452	-124.22242*	-111.43790*
Std. Error	-	-	-	-	34.94437	25.03306	36.34571
Sig.	-	-	-	-	0.715	0.000	0.003

\*. The mean difference is significant at the 0.05 level

Table 2 Show the level of Insulin in obese ,overweight children and normal. The correlation is significant between obese and normal weight children.

**Table (2): Mean, standard deviation, standard error of Insulin in healthy obese, over weight and normal children**

Group	Mean	Number	Stander Deviation	Median	Obese / Over Weight	Obese / Normal	Over Weight / Normal
Obese	23.1258	40	27.52240	3.71922	-	-	-
Over Weight	12.1955	11	4.89210	1.47502	-	-	-
Normal	11.6886	29	2.71304	0.50380	-	-	-
Mean Difference	-	-	-	-	10.93030	11.43713*	0.50683
Stander Error	-	-	-	-	5.75790	4.12478	5.98880
Significant	-	-	-	-	0.06	0.007	0.933

\*. The mean difference is significant at the 0.05 level.

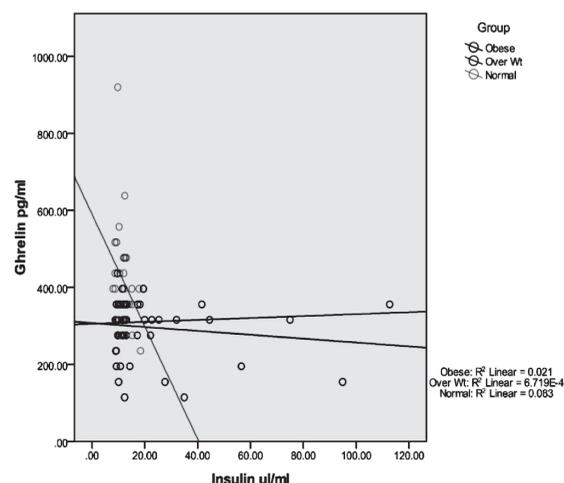
Table 3 Show Pearson correlation between ghrelin and Body mass index ,Insulin

**Table(3) : Pearson correlation between ghrelin and Body mass index ,Insulin**

	Group	BMI	Insulin
Ghrelin	Pearson Correlation	-.454- **	-.217
	Sig. (2-tailed)	.000	.053
	N	80	80

\*\* .The mean difference is significant at 0.05 leve

Figure 1 show correlation between Ghrelin and Insulin among obese, over weight and normal weight children.



**Figure (1) correlation between Ghrelin and Insulin among obese, over weight and normal weight children**

**Discussion:**

In table (1) , the mean value of Ghrelin shows a significant difference between obese / overweight and normal weight children, being low in obese ( Mean 295 Pg/ml) and overweight (Mean 308 Pg/ml), while high in normal weight children (Mean 420 Pg/ml ,  $P < 0.000$  ). These data demonstrated that Ghrelin is involved in the control of appetite and energy balance.

Since Ghrelin acts as a ligand for the hypothalamic and pituitary GHS-RIa and exerts an orexigenic activity through the NPY/AGRP system and the orexin pathway (10). Ghrelin appears to have a role as a long-term signal of nutritional status opposite to that of leptin. Systemic ghrelin levels are negatively associated with body adiposity and increase with weight loss induced by low-calorie diet, exercise, anorexia nervosa, or cachexia as a result of organ failure (cardiac, pulmonary, renal, or hepatic) or malignancy.(11). Also Ghrelin leads to increased gastrointestinal motility and (possibly) increased gastric acid secretion, which may be physiologically relevant in preparing the gastrointestinal tract to process food. (12). In another study, significant differences were found in ghrelin levels at 3 hours; ghrelin levels began recovery to baseline levels within 3 hours after food intake among obese compared to healthy children whose levels remained suppressed after 3 hours. (13) In table (2), the mean value of Insulin shows significant difference between obese and normal weight children being high in obese while low in normal weight children (Mean 11.6886 ,  $P < 0.000$  ). These results showed that the obese children will predispose to insulin resistance and development of DM.Circulating levels of insulin positively correlate with adipose tissue mass within the body. Insulin implicated in the long-term regulation of energy balance. Insulin is synthesized in the  $\beta$  cells of the pancreas and is secreted rapidly after a meal, with well characterised hypoglycaemic effects (14). However, insulin also acts as an anorectic signal within the CNS. Insulin enters the CNS through a saturable and receptor-mediated transport process (15). Insulin receptors are widely expressed in the brain, particularly in hypothalamic nuclei, such as the ARC, DMN, and PVN, which are involved in control of food intake. Although the mechanism of insulin-mediated anorexia has not been fully elucidated, hypothalamic NPY seems to be involved (16). In Table 3 showed a negative correlation between Ghrelin and Insulin some but not all studies support the concept that insulin is an inhibitor of ghrelin secretion. Thus, obesity-related hyperinsulinemia could at least in part be responsible for ghrelin suppression (13). This finding agrees with the available data that suggest a negative association between systemic ghrelin and insulin levels.(14) Ghrelin inhibits insulin secretion both in vitro and in most human or animal studies.(15) However,

other studies have suggested that ghrelin may stimulate insulin secretion in certain paradigms. In addition, it is not clear whether endocrine or paracrine effects of ghrelin are more physiologically relevant in the regulation of insulin secretion (16). Ghrelin inhibits insulin effects on glycogen synthesis and gluconeogenesis in vitro.(14) Ghrelin may also inhibit secretion of the insulin-sensitizing protein adiponectin from adipocytes and stimulate secretion of the counter-regulatory hormones, including GH, cortisol, epinephrine, and (possibly) glucagon.(16) More studies are needed to fully elucidate the precise physiologic role of ghrelin on the regulation of glucose homeostasis. The mechanisms by which ghrelin could inhibit insulin secretion are unknown. Ghrelin may exert a direct effect on the  $\beta$ -cell or act indirectly by stimulating the secretion of counter-regulatory hormones that affect insulin secretion, or activating neural pathways that regulate islet function (17). The signaling mechanisms for insulinostatic ghrelin action in islet  $\beta$ -cells have been explored. Both endogenous and exogenous ghrelin has been shown to attenuate glucose-induced insulin release via  $G\alpha_{12}$ - mediated activation of Kv channels, and suppression of action potential firing and  $[Ca^{2+}]_i$  increases in  $\beta$ -cells (18).

**Conclusions:**

This study showed that ghrelin reduces insulin secretion and glucose disappearance in healthy children. This findings raise the possibility that endogenous ghrelin has a role in physiologic insulin secretion, and that ghrelin antagonists could improve  $\beta$ -cell function.

**Author contribution:**

Zena E. Noor Aldeen: data analysis, interpretation of data , drafting of manuscript.

Prof. Dr Hedef Dhafir EL-Yassin: study conception, design,critical revision.

Prof. Dr. Mahjoob Naffil Al Naddawi: critical revision.

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