Original Article

Effect of the co-administration of glucose with morphine on glucoregulatory hormones and causing of diabetes mellitus in rats

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Abstract

Background: Morphine is related to dysregulation of serum hormone levels. In addition, addict subjects interest to sugar intake. Therefore, this study investigated the effect of co-administration of glucose with Mo on the glucoregulatory hormones and causing of diabetes mellitus in rats.

Materials and Methods: Male rats were randomly divided into four groups including, control, morphine, Morphine-Glucose and diabetes groups. Morphine was undergone through doses of 10, 20, 30, 40, 50, and 60 mg/kg, respectively on days 1, 2, 3, 4, 5, and 6. Then, dose of 60 mg/kg was used repeated for 20 extra days. The Morphine-Glucose group received the same doses of morphine plus 1 g/kg glucose per day. Diabetes was induced by intraperitoneal injection of 65 mg/kg streptozotocin. At the end of experiment, the serum insulin, glucagon, growth hormone (GH), cortisol, and glucose levels were measured. The homeostasis model assessment (HOMA) indexes concluding the HOMA-insulin resistance (HOMA-IR) and HOMA-β were evaluated.

Results: Morphine insignificantly induced a hyperglycemia condition and insulin resistance. Whereas, the beta-cell functions significantly ($P < 0.05$) decreased only in morphine group. The co-administration of glucose slightly increased the GH, and increased insulin and cortisol levels significantly ($P < 0.05$ and $P < 0.01$; respectively) in the Morphine-Glucose group. Furthermore, the co-administration of glucose with morphine could nearly modulate the morphine effects on body weight, glucose, and glucagon levels.

Conclusion: It is probable that the co-administration of glucose with morphine modulate the serum glucose levels by stimulating the beta-cell functions and to increase insulin secretion.

Key Words: Cortisol, diabetes mellitus, glucagon, growth hormone, insulin, morphine

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INTRODUCTION

The prevalence of addiction to opioids and diabetes has increased in human societies and it is the major health challenge in the world today. Recent studies have shown that morphine directly affects the endocrine system and neurotransmission of the central nervous systems.[1] In addition, endogenous morphine is present as a neurotransmitter and neuroendocrine mediators in the brain.[2-4] Therefore, morphine could

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be one of the predisposing factors that contribute in beginning of disease. Previous studies demonstrated that opiate had various effects on glucose hemostasis and possibility on the levels of many glucoregulatory hormones.[5-7] Hence, this may be especially important in causing of insulin resistance (IR) and even diabetes mellitus (DM). IR is the first phase in type 2 diabetes progression that often results in hyperinsulinemia, disruption of glucose, and lipid metabolism.[8] Some of the previous studies have reported that morphine increased levels of glycosylated hemoglobin in addicts, similar to that seen in diabetics.[9] Furthermore, addict subjects interest to sugar intake that associates with changes of metabolism regulation.[10] Therefore, co-administration of glucose with morphine may change serum hormone levels and glucose in addict subjects. Therefore, the aim of the present study was to evaluate the effect of long-term co-administration of glucose with morphine on levels of serum glucoregulatory hormones, serum glucose level, and its possible links with causing DM in rats.

MATERIALS AND METHODS

Experimental animals

Experiments were performed on 32 male Wistar rats with an initial weight of 250–300 g obtained from the Pasteur Institute, Tehran, Iran. All experimental protocols were approved by the Ethical Committee of Isfahan University of Medical Sciences (Isfahan, Iran) in compliance with the "Principles of Laboratory Animal Care" and the European Communities Council Directive of 24 November 1986 (86/609/EEC). Rats were housed in a light-controlled condition (12-h light/dark; lights on 07:00–19:00) in a room with a temperature of 22 ± 2°C. Food and water available *ad libitum*. In addition, duration of experiments was 26 days. Rats were randomly assigned to four groups (n = 8 in each) as follows:

- Control (Co) group: Rats were with no special treatment and received saline
- Morphine (Mo) group: Rats received morphine
- Morphine-Glucose (Mo-Glu) group: Rats received the same dose of morphine plus 1 g/kg glucose per day
- Diabetes mellitus (DM) group: Rats were received the streptozotocin for inducing of DM.

Experimental procedures

Drugs

In the current study, addiction was induced by intraperitoneal (i.p) injection of progressive doses of morphine sulfate (Temad Co., Tehran, Iran) by dissolving in saline 0.9%. Morphine sulfate was undergone through doses of 10, 20, 30, 40, 50, and 60 mg/kg, respectively on days 1, 2, 3, 4, 5, and 6.[11] Then dose of 60 mg/kg was used repeated for 20 extra days in rats. The Mo-Glu group received the same doses of morphine plus 1 g/kg glucose per day. The positive urine morphine was detected using Acon® urine morphine test strip (Health Research Systems Inc., USA).

Diabetes was induced by a single i.p injection of streptozotocin (STZ; 65 mg/kg; Sigma Co., USA) dissolved in saline 0.9% and the success was checked by both serum glucose levels and the positive urine glucose was monitored using Uri SCAN glucose strip (YD Diagnostics Co., Korea).[12,13] There are urine test strips for assessment of increased glucose levels in the urine. Hence, urine samples were collected and tested using a dipstick that changes color according to the amount of glucose present. Then, the dipstick is compared to a color chart. High glucose levels in the urine indicate DM.

Assessment of serum glucose levels

At the end of the experiments, animals were sacrificed at 8:00–10:00 by decapitation on day 27. Their fasted blood samples were obtained from the trunk blood; serum was separated by centrifugation (6000 rpm, 20 min) and stored at –80°C until analysis. The serum glucose level was measured by the glucose oxidase method (Parsazmun Co., Iran).

Assessment of hormonal levels

Following decapitation of animals, the commercial enzyme-linked immunosorbent assay (ELISA) kits (Zellbio Co., Germany) was used to assess all of serum glucoregulatory hormones such as glucagon, insulin, cortisol, and growth hormone (GH) levels.

Assessment of insulin resistance and beta function

IR is a main factor in pathogenesis of type II diabetes.[8] IR was calculated by homeostasis model assessment (HOMA) using the formula homeostasis model assessment-IR (HOMA-IR) = Fasting insulin (μU/ml) × fasting glucose (mg/dl)/22.5. The high-HOMA values indicate IR or low insulin sensitivity.[14,15] On the other hand, there is a feedback loop between the insulin-sensitive tissues and the β-cells. The β-cells increase insulin secretion in response to demand by the liver, muscles, and adipose tissue.[16] Furthermore, the HOMA for β-cell function (HOMA- β) calculated by homeostasis assessment model using the formula HOMA-β = (360– Fasting insulin [mU/ml])/(Fasting glucose [mg/dl] –63).

Measurement of body weight differences

Animals' body weights were measured on the days 1 and 26 of the experiment. The body weight differences (BWD = BW_{Day26}– BW_{Day1}) was measured.

Data analysis

All data were analyzed by ANOVA followed by both Tukey's and Fisher's least significant difference (LSD) *post-hoc* tests for multiple groups. In this research, values are reported as mean ± standard error of the mean, where $P < 0.05$ is considered statistically significant. Ultimately, the calculations were performed using SPSS 21 software (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Assessment of serum glucose levels

Based on the ANOVA and *post-hoc* Tukey's results, there were insignificant increases in the serum glucose level of the Morphine (Mo) and the Morphine-Glucose (Mo-Glu) groups (24.14% and 6.29%; respectively) compared to the Control (Co) group [Figure 1]. It indicated that glucose intake in the addict group nearly modulated serum glucose level.

As shown in Figure 1, the glucose level of the Mo-Glu group showed insignificant decreases (14.38%) compared to the Mo group, suggesting it is probable that the glucose usage in the addict rats decreased the serum glucose levels with respect to morphine administration alone.

In diabetic (DM) group, the serum glucose level was significantly higher ($P < 0.001$) than those in the Co., Mo and Mo-Glu groups (5.78, 4.65, and 5.43 folds; respectively) [Figure 1].

Assessment of serum glucagon levels

Results demonstrated insignificant decreases in the serum glucagon levels of the Mo and the MO-Glu (20.16% and 12.22%; respectively) compared to the Co group [Figure 2].

In addition, there was an insignificant increase (9.94%) in the glucagon level of the Mo-Glu group compared to the Mo group [Figure 2].

Serum glucagon level had a significant ($P < 0.001$) enhancement in the DM group compared to the Co., Mo and Mo-Glu groups (2.44, 3.06 and 2.78 folds; respectively) [Figure 2].

Assessment of serum insulin levels

The serum insulin level in the Mo group had not significantly enhancement (3.58 %) from that in the Co group. Whereas, the insulin level in Mo-Glu group showed significantly ($P < 0.05$; 39.79 %) increases compared to the Co group [Figure 3].

As shown in Figure 3, the insulin level in the Mo-Glu group showed slightly enhancement (34.95%) compared to the Mo group.

In the DM group, insignificant differences were identified in the insulin levels compared to the Co and Mo groups (7.17% and 10.39%; respectively). Whereas, insulin level of DM group was significantly ($P < 0.05$, 33.6%) lower than that in the Mo-Glu group [Figure 3].

Assessment of serum cortisol levels

There were significant enhancements in the serum cortisol level of the Mo ($P < 0.05$; 11.55%) and the Mo-Glu groups ($P < 0.01$; 16.57%) compared to the Co group [Figure 4].

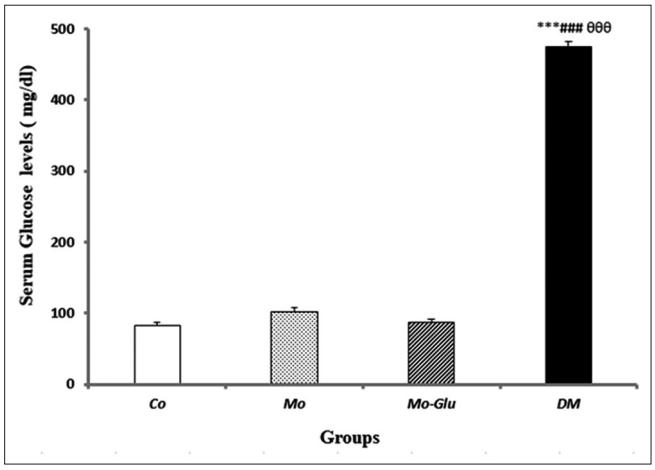

Figure 1: Comparison of serum glucose levels in different groups. Results are expressed as mean ± standard error of the mean (ANOVA test, Tukey's *post-hoc* test; $^{***}P < 0.001$ when compared to the control group group; $^{###}P < 0.001$ and $^{θθθ}P < 0.01$ when compared to the Mo-Glu group). Co: Control group; Mo: Morphine group; Mo-Glu: Morphine-Glucose group; DM: Diabetes mellitus group

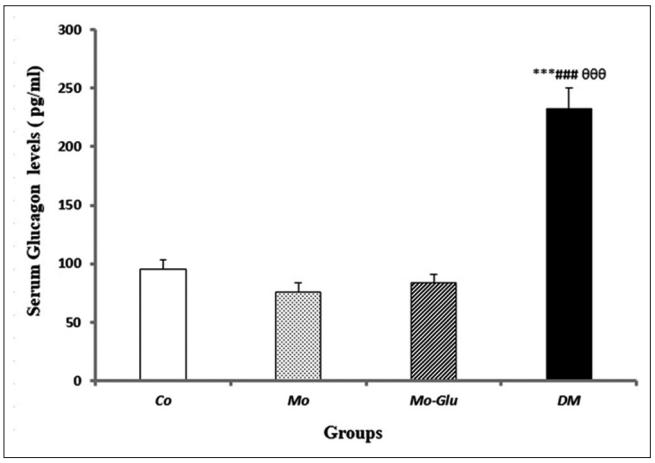

Figure 2: Comparison of serum glucagone levels in different groups. Results are expressed as mean ± standard error of the mean (ANOVA test, Tukey's *post-hoc* test; $^{***}P < 0.001$ when compared to the control group group; $^{###}P < 0.001$ and $^{θθθ}P < 0.01$ when compared to the Mo-Glu group). Co: Control group; Mo: Morphine group; Mo-Glu: Morphine-Glucose group; DM: Diabetes mellitus group

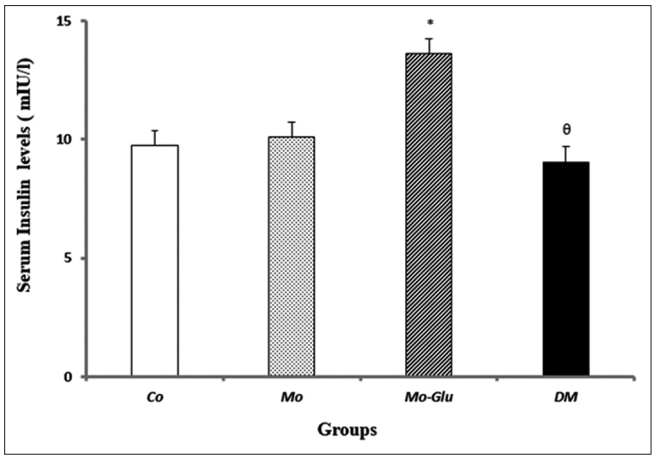

Figure 3: Comparison of serum insulin levels in different groups. Results are expressed as mean ± standard error of the mean (ANOVA test, Tukey's *post-hoc* test; **P* < 0.05 when compared to the Co group and $^{\theta}P$ < 0.05 when compared to the Mo-Glu group). Co: Control group; Mo: Morphine group; Mo-Glu: Morphine-Glucose group; DM: Diabetes mellitus group

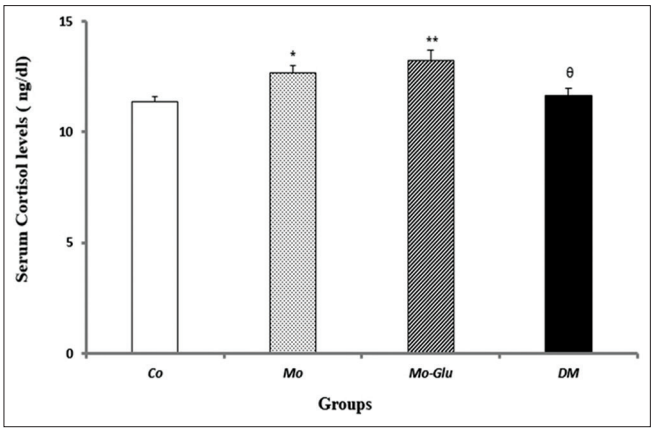

Figure 4: Comparison of serum cortisol levels in different groups. Results are expressed as mean ± standard error of the mean (ANOVA test, Tukey's *post-hoc* test; **P* < 0.05 and ***P* < 0.01 when compared to the Co group and $^{\theta}P$ < 0.05 when compared to the Mo-Glu group). Co: Control group; Mo: Morphine group; Mo-Glu: Morphine-Glucose group; DM: Diabetes mellitus group

As shown in Figure 4, the cortisol level of the Mo-Glu group showed insignificant increases (about 4.5%) with respect to the Mo group.

In the DM group, the serum cortisol levels showed insignificant increases and decreases (2.46% and 8.14%; respectively) compared to the Co and Mo groups. Whereas the cortisol levels of the DM group was significantly ($P < 0.05$; 12.10%) lower than that in the Mo-Glu group [Figure 4].

Assessment of serum growth hormone levels

The GH level in the Mo and the Mo-Glu groups had not significantly decreases and enhancement (2.36% and 16.58%; respectively) from that in the Co group [Figure 5].

As shown in Figure 5, the GH level in the Mo-Glu group showed insignificant increases (19.41%) in the Mo group.

Serum GH levels had insignificant increases in the DM group compared to the Co and the Mo groups (5.21% and 7.76%; respectively). Furthermore, the serum GH level showed insignificant decreases (9.75%) in the DM group compared to Mo-Glu group [Figure 5].

Assessment of insulin resistance and beta cell function

Results demonstrated insignificant increases in the HOMA-IR of the Mo and the MO-Glu (31.07% and 46.89%; respectively) compared to the Co group [Figure 6].

In addition, there was an insignificant increase (12.06%) in the HOMA-IR of the Mo-Glu group compared to the Mo group [Figure 6].

HOMA-IR had a significant ($P < 0.001$) enhancement in the DM group compared to the Co, Mo and Mo-Glu groups (5.39, 4.12 and 3.67 folds; respectively) [Figure 6].

There was a significant decrease in the HOMA-B of the Mo ($P < 0.05$; 2.76-fold) compared to the Co group. The HOMA-B of the Mo-Glu group showed insignificant increases (18.88%) with respect to the Mo group [Figure 7].

The HOMA-B of the DM group was significantly ($P < 0.01$ and $P < 0.05$; respectively) lower than that in the Co and the Mo-Glu (34.95 and 28.35 folds; respectively) groups [Figure 7].

Assessment of body weight difference

The BWD = BW_{Day26} – BW_{Day1} in the Mo group, was significantly ($P < 0.01$, 2.47-fold) lower than the Co group. Meanwhile, insignificant decreases (1.55-fold) were observed between the Mo-Glu and the Co groups in the BWD [Figure 8].

The results indicated insignificant increases (37.19%) in the BWD of the Mo-Glu group compared to Mo group [Figure 8]. It suggested the co-administration of glucose with morphine could improve body weight loss in addict group.

In the DM group, the BWD was significantly ($P < 0.001$, $P < 0.01$ and $P < 0.01$; respectively) lower than the Co, Mo and Mo-Glu groups (6.64, 2.68 and 4.27 folds; respectively) [Figure 8].

DISCUSSION

In the current study, chronic morphine usage did not lead to diabetes. Addiction insignificantly induced

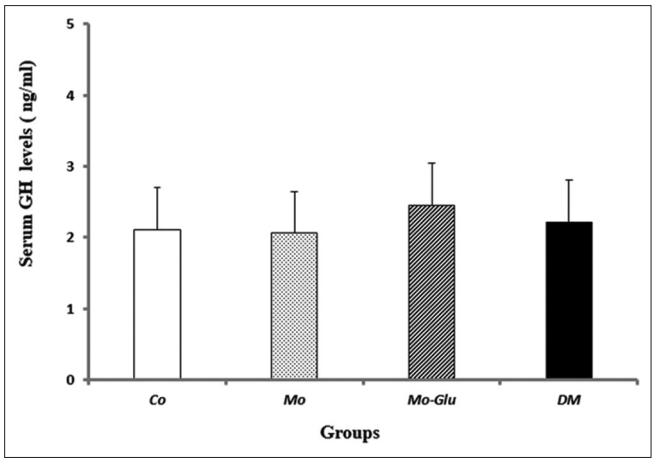

Figure 5: Comparison of serum growth hormone levels in different groups. Results are expressed as mean ± standard error of the mean (ANOVA test, Tukey's *post-hoc* test. All data were no significant. Co: Control group; Mo: Morphine group; Mo-Glu: Morphine-Glucose group; DM: Diabetes mellitus group

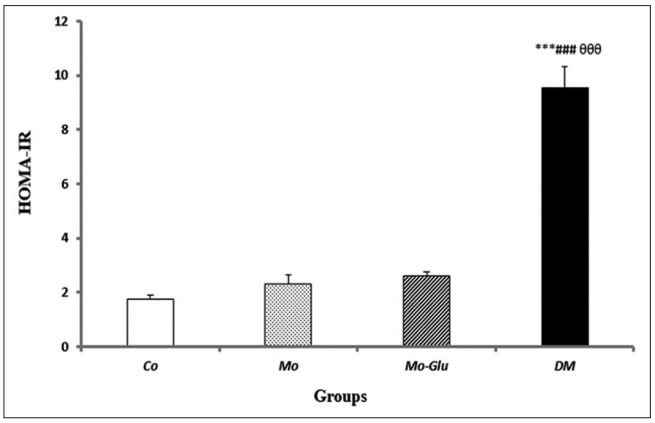

Figure 6: Comparison of homeostasis model assessment for insulin resistance (HOMA-IR) in different groups. Results are expressed as mean ± standard error of the mean (ANOVA test, LSD *post-hoc* test; ***P < 0.001 when compared to the Co group; ###P < 0.001 when compared to the Mo group and $^{\theta\theta\theta}P$ < 0.001 when compared to the Mo-Glu group). Co: Control group; Mo: Morphine group; Mo-Glu: Morphine-Glucose group; DM: Diabetes mellitus group

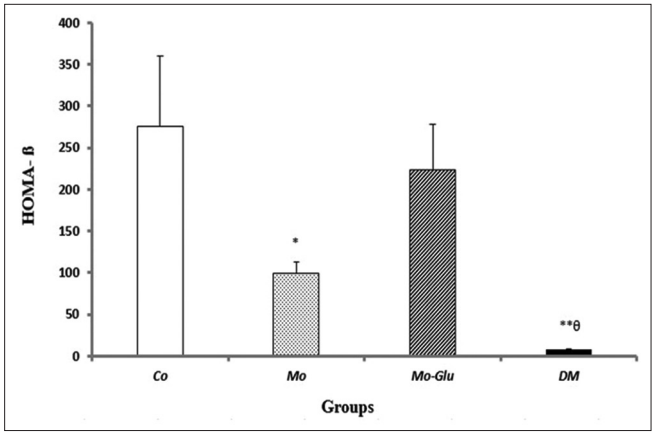

Figure 7: Comparison of homeostasis model assessment for β-cell function (HOMA- β) in different groups. Results are expressed as mean ± standard error of the mean (ANOVA test, LSD *post-hoc* test;*P < 0.05 and **P < 0.01 when compared to the Co group; $^{\theta}P$ < 0.05 when compared to the Mo-Glu group). Co: Control group; Mo: Morphine group; Mo-Glu: Morphine-Glucose group; DM: Diabetes mellitus group

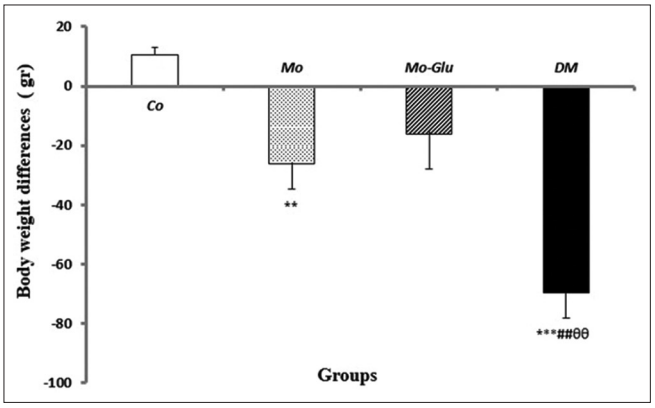

Figure 8: Comparison of body weight differences in different groups. Results are expressed as mean ± standard error of the mean (ANOVA test, Tukey's *post-hoc* test; **P < 0.01 and ***P < 0.001 when compared to the Co group; ###P < 0.001 when compared to the Mo group and $^{\theta\theta}P$ < 0.01 when compared to the Mo-Glu group). Co: Control group; Mo: Morphine group; Mo-Glu: Morphine-glucose group; DM: Diabetes mellitus group

hyperglycemia and IR. Whereas, the beta-cell function significantly decreased in the Mo group. These differences may be clearer by the passage of time and more morphine dose administration. Therefore, it is possible that morphine can cause diabetes in the per-diabetic subject or even in individual with genetic background. It is concluded that the slight hyperglycemia, due to morphine might have been either a result of effective glucoregulatory hormone secretions, or inhibiting the glucose clearance. Previous studies reported that high dose of morphine caused hyperglycemia by increasing hepatic rate of glucose production and decreases of glucose clearance by the peripheral tissues.[9,17] Whereas, other studies indicated that morphine redacted serum glucose and disappeared glucose from the urine,[18-20] probably by influencing the renal threshold for glucose.[18] In addition, one of the previous studies demonstrated that morphine created IR by increasing glucose and decreasing glycolytic enzyme's function.[21] Therefore, the effect of morphine on glucose and hormone levels was reported differently. It seems that these differences may be due to the administration doses, kinds of opiate, types of injection, strain, and the duration of morphine usage.[22]

According to the present data, the co-administration of glucose with morphine caused a slight decrease in induced hyperglycemia with respect to morphine alone. It seems that the glucose intake in addict rats probably caused a better use of blood glucose and/or more storage of glucose in longer duration; however,

it was not manifest. It has probably happened by effect of hormone receptors and glucose transporters on some organs, also the synthesis of glycogen in the liver and muscle. In addition, in the present study, the co-administration of glucose with morphine did not cause IR by the evaluation of HOMA-IR. Whereas, only the HOMA-B (beta-cell function) increased in this group compared to morphine administration. It is probable that glucose intake modulated the serum glucose level by stimulating of beta-cell functions and particularly increases of insulin secretion. It was indicated in one of previous studies that various dosages of morphine enhance the serum insulin level.[23] Hosseini reported that morphine administration elevated glucose level by the entry of more glucose into pancreatic beta-cells through an increase in the rate of glycolysis. Therefore, it can improve insulin secretion.[23] Different mechanisms may be involved in the enhancements of insulin secretion by morphine such as the enhancement of the adrenaline[5] and insulin growth factor levels,[24,25] inhibition of the Somatostatin's secretion,[26] closing K_{ATP} channels by glucose,[27,28] affecting both sympathetic and parasympathetic nervous systems.[29] In addition, the long-term administration of morphine reduces leptin receptors.[30,31] The increased serum leptin level decreases insulin sensitivity in some tissues, and the function of pancreatic beta-cells becomes deficient[32] and hyperinsulinism occurs.[31,33] On the contrary, Ferenczi *et al*. reported that the insulin plasma level was lower in morphine user with respect to normal group.[19]

In the current study, the serum glucagon and the GH levels showed no remarkable difference in both of addict groups. In agreement with our finding, Reid *et al*. reported that endorphin acts without altering basal levels of GH.[34] Some studies reported that opiates inhibit somatostatin secretion and so inhibits GH secretion.[26,34] Whereas, in the current study, the cortisol level significantly increased in the Mo group and particularly the Mo-Glu group compared to control group; however, it caused slight hyperglycemia. Bossone and Hannon also reported elevated cortisol level by morphine administration.[35] In contrast, it was reported that the opiate administration raised serum GH level; however, decreased serum cortisol level.[36] Hence, based on all the presented hormonal data, it concluded that the cortisol secretion was one of the possible important mechanisms for the slightly hyperglycemic response of morphine. Hepatic glucose output in the liver may be increased On the other hand, it seems that the co-administration of glucose with morphine might stimulate the renal glucose clearance and/or increased storage of it.

In general, the reduction of body weight was observed in all addict groups. Ferenczi *et al*. also reported weight loss by the morphine administration.[19] Whereas, another study demonstrated acute administration of morphine increased food intake and weight gain.[37] In the current study, the co-administration glucose with morphine modulated the glucose and glucagon levels. In addition, it slightly increased the GH, and increased insulin and cortisol levels significantly. Hence, it could nearly compensate body weight loss in addicted subjects. Therefore, in addict rats, it is possible that glucose intake modulated uptake and storage of glucose, also to change secretion rate for other hormones such as somatostatin and leptin is only compared to morphine administration.

In diabetic rats, the cortisol and GH levels showed no remarkable enhancement and decreases, respectively. It is possible that diabetic rats had adapted with diabetes. Busiguina *et al*. indicated decreased body weight and GH level in diabetic rats.[38] In addition, body weight loss may be related to decreased glycogen storage, the GH and insulin levels and/or enhancement of cortisol and glucagon levels in diabetic rats.

CONCLUSION

The co-administration of glucose with morphine can probably modulate the effects of morphine on physiologic system. Moreover, it is probable that the co-administration of glucose with morphine modulate the serum glucose levels by stimulating the beta-cell functions and to increase insulin secretion. Accordingly, the evaluation of other factors, which are possibly involved in glucose homeostasis such as muscle and glycogen storage, is highly recommended.

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Conflicts of interest

There are no conflicts of interest.

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