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Original Research

Short-term administration of high dose dexamethasone can induce maximum insulin resistance in Wistar albino rats

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Abstract

Background: Long-term administration of dexamethasone induces adverse effects such as muscle catabolism, hyperplasia, increased adiposity, and insulin resistance (IR). In view of these data, many authors tried to induce IR with different individual dose ranges with a varied induction periods. In this study, dexamethasone was used to find the dose to induce maximum insulin resistance in rodents. **Materials and methods:** A sum of 42 healthy male Wistar albino rats were categorized into six groups of dexamethasone treatment and one control group (n=6/group). In a 6-day study period, all treatment groups received respective graded doses of dexamethasone starting from low – (0.5 mg/kg and 1 mg/kg), intermediate – (2 mg/kg and 4 mg/kg) and high-dose (8 mg/kg and 16 mg/kg). **Results:** Graded doses of dexamethasone treatment for 6 days produced hyperglycemia and hyperinsulinemia in a dose-dependent manner and the maximum effect was noted with high doses of dexamethasone compared to intermediate and low ($p<0.05$). The profound reduction in insulin sensitivity was caused by high-doses of dexamethasone treatment evidenced by sustained elevation of homeostatic model assessment of insulin resistance (HOMA-IR) which was strongly associated with a declined homeostatic model assessment of insulin sensitivity (HOMA-IS), The peripheral sensitivity indices, Gutt and Matsuda, were markedly elevated in high dexamethasone groups compared to intermediate- and low-dose groups ($p<0.05$). Serum lipids and creatinine ($p<0.05$), whereas high-density lipoprotein cholesterol (HDL-CH) was markedly reduced and resulted in the subsequent rise in the atherogenic index (AGI) ($p<0.05$). Moderate to severe glycosuria and ketonuria were noted in intermediate- and high-dose treatment groups only. However, there is no significant difference in metabolic effects between 8 mg/kg and 16 mg/kg treatments ($p>0.05$). **Conclusion:** Administration of 8 mg/kg dexamethasone for 6 days would be sufficient for the induction of maximum insulin resistance in Wistar albino rats.

Keywords: HOMA, insulin resistance, hyperglycemia, hyperinsulinemia, metabolic effects.

Background and aims

Glucocorticoids can cause insulin resistance (IR) and lipid abnormalities on long-term use [1] and which may result in the development of type II diabetes, cardiovascular diseases, hypertension, polycystic ovary disease, non-alcoholic fatty liver disease, etc. [2]. They can also affect electrolytes and water excretion because of their mineralocorticoid action in experimental animals. Dexamethasone (Dex) is a long-acting glucocorticoid and devoid of mineralocorticoid activity, relative to cortisol. It has many therapeutic applications in clinical practice which include anti-inflammatory and immunosuppressant actions. Dex in excess or its chronic usage results in unwanted effects such as muscle catabolism, increased adiposity, and increased insulin resistance.

Although, the currently available insulin resistance animal models are less relevant to the

pathological process of insulin resistance caused by the natural multi-factorial process, thus limiting the screening of agents that controls only the level of blood glucose [3]. It is most important to develop insulin resistance animal models that mimic the natural pathological process of insulin resistance. The literature revealed, many authors have tried dex to induce insulin resistance in rodent models to have a better understanding of the pathophysiological process of insulin resistance and to develop insulin sensitizers [4]. But there is an uncertainty in terms of duration and dosage chosen. The present study is aimed to determine the appropriate dose of dexamethasone and the duration to induce maximum insulin resistance in rodents.

Table 1: grouping of animals and administration of graded doses of dexamethasone to respective groups.

Groups	Dose of dexamethasone (mg/kg BW/i.p)	n
Control	Normal saline	6
I	0.5	6
II	1	6
III	2	6
IV	4	6
V	8	6
VI	16	6

Note: i.p=intraperitoneal route.

Materials and methods

An average body weight (250–275 g), male Wistar albino rats have been reared individually in polypropylene cages at 23–25°C with 12 hours light: 12 hours dark cycle with access to standard food pellets and water *ad libitum* for 15 days. All the experimental animals were acclimatized for 15 days prior to the initiation of the experiment. The ethical clearance (Letter no: AEC/29//2017) for the proposed study was obtained from the IAEC, KS Hegde Medical Academy, Karnataka, India.

Grouping of animals

As shown in (Table 1), graded doses of dex were chosen starting from low (0.5 mg/kg and 1 mg/kg), intermediate (2 mg/kg and 4 mg/kg) and high doses (8 mg/kg and 16 mg/kg), to demonstrate the dose-dependent metabolic effects of insulin resistance. A sum of 42 healthy male Wistar albino rats was allocated into six groups of dexamethasone treatment and one control group with six animals in each group.

Procedure

According to the bodyweight of each animal, doses of dexamethasone have been administered through the intraperitoneal route (i.p) for 6 days. Each rat was allowed to have only standard food pellets and water up to the 5th day evening *ad lib*. Followed by overnight fasting, on day six, dex was given as per the drug schedule, collected fasting blood samples by retro-orbital sinus puncture method under ether anesthesia by open drop method. The collected fasting samples were processed for estimating fasting blood sugar (FBS), Fasting insulin, and serum lipids. A glucose tolerance test (IPGTT) was carried out in all rats by administering i.p glucose (2 gm/kg body weight) as per the body weight. At intervals of 30 minutes, 60 minutes, and 120 minutes of post-IPGTT, blood samples were collected and processed for the estimation of glucose and insulin [5]. Both fasting and post-IPGTT samples were centrifuged at 4000 RPM/20 minutes for serum and processed for biochemical estimation (fasting glucose, serum lipids, and insulin).

Estimation of serum glucose

Serum glucose level was estimated in mg/dl according to the GOD-PAP method and it was expressed as Mean±SD [6].

Estimation of serum insulin

ELISA insulin estimation kit which is ultra-sensitive for rats [7] was bought from Crystal Chem labs, New Delhi. A high range assay was

conducted (1–64 ng/ml) to obtain the insulin values with the provided reagents and serum samples. The microplates coated with the antibody reagent and marked 'A' was fixed to the Elisa frame. Each well was filled with 95 µl of sample diluent that was marked 'G' and 5 µl of the sample. The microplate was kept in incubation for 2 hours at 4°C. After the incubation period, each well was washed five times with wash buffer solution. Anti-insulin enzyme conjugate, 100 µl per well was dispensed and the microplate was kept in incubation for half-an-hour at room temperature. Later, each well was washed seven times with a buffer solution. Enzyme substrate solution marked 'E', 100 µl per well was dispensed. Then, the microplate was again incubated for 10 minutes at room temperature in a light-free area. The enzyme reaction stop solution marked 'F', 100 µl per well was added to stop the enzyme reaction. With the help of standard curves, optical density values were obtained. The optical density values were later converted to their original insulin values (µU/ml) by using a linear regression equation in MS Excel 2013 version. The data were represented as Mean±SD.

Quantification of insulin resistance /sensitivity surrogate indices

Formulas used for estimating indices:

HOMA-IR= *fasting insulin* ×*fasting glucose* ÷405

HOMA-IS= 10000÷*fasting insulin* ×*fasting glucose* [8]

$$\text{Gutt index} = \text{ISI}_{0,120} = \frac{500+(G0-G120)\times 0.19\times body\ wt}{120\times G\ mean\times log(I\ mean)} \quad [9]$$

$$\text{Matsuda index ISI}_{(\text{Matsuda})} = \frac{10000}{\sqrt{G0\times I0}\times G\ mean\times I\ mean} \quad [10]$$

Atherogenic index (AGI) = HDLC-CH/HDLC [11]

The homeostatic model assessment (HOMA) was employed to understand the degree of hepatic insulin resistance (IR) and sensitivity (IS). Peripheral IS was determined by the Gutt index whereas, the whole body IS was assessed by the Matsuda index. Further, AGI was determined to assess the risk of atherogenesis.

Lipid profile (HDL, LDL, VLDL, TGs, and CH)

The lipid profile was determined by using standard laboratory reagents, reagent kits, and an automatic analyzer. The HDL cholesterol was determined by phosphotungstate magnesium acetate precipitation method, triglycerides (TGs) were determined by GPO-PAP method and the serum total cholesterol (CH) was determined by Oxidase peroxidase method.

The VLDL and LDL were determined by using standard formulae, as follows VLDL=triglycerides/5 and LDL=total cholesterol – [HDL cholesterol – triglycerides/5], respectively [11].

Urine glucose and ketones

The fasting samples of urine were collected on day 12th morning in sample containers and the presence of glucose and ketones were determined by (uristix) dipstick method [12].

Statistical analysis

Data were represented as Mean±SD and One-way ANOVA was used for comparison and Post-hoc Scheffe multiple comparison tests were also employed. Statistical significance was assumed at the 5% level of significance and $P<0.05$ was considered as significant.

Results

Dose-dependent effect of dexamethasone on food intake, body weight, and water intake

The dose-dependent effect of dexamethasone on food intake, body weight, and water intake of rats in respective treatment groups was recorded. The rats treated with low doses (0.5 mg/kg and 1 mg/kg) showed mild reduction in body weights and as the doses were increased the reduction of body weights was also more marked correspondingly. A maximum of [109.5±4.2 g] 31.9% reduction in body weights from day 7 to day 12 with 16 mg/kg and [102.8±6.6 g] 31.6% of

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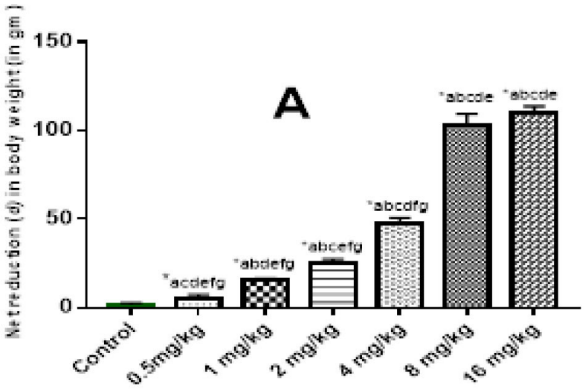
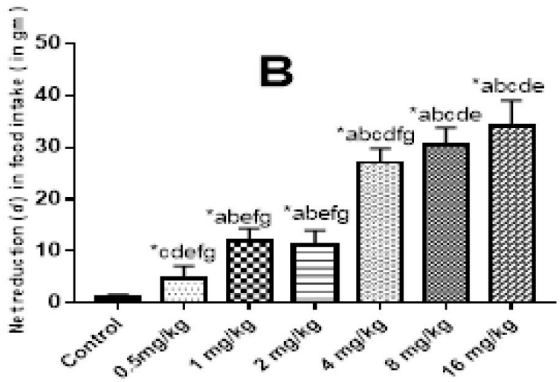
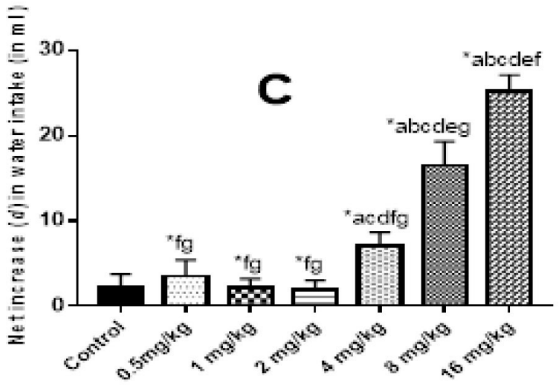
reduction with 8 mg/kg of dexamethasone treatment which were highly significant ($p<0.05$) compared to remaining dexamethasone doses but, the difference was insignificant ($p>0.05$) between 8 mg/kg and 16 mg/kg treatments (Figure1A). At a dose of 16 mg/kg, dexamethasone produced a maximum of [34.3±4.8 g] 91.9% reduction and 8 mg/kg dexamethasone produced [30.6±3.2 g]



Note: *= significant at the level of 5% (P= < 0.05), *d* = reduction in body weights in dexamethasone and control groups between day 7 and day 12; a= PC; b=0.5mg/kg; c=1mg/kg; d=2mg/kg; e=4mg/kg; f=8mg/kg; g=16mg/kg.



Note: *= significant at the level of 5% (P= < 0.05), *d* = reduction in food intake in dexamethasone and control groups between day 7 and day 11; a= PC; b=0.5mg/kg; c=1mg/kg; d=2mg/kg; e=4mg/kg; f=8mg/kg; g=16mg/kg.



Note: *= significant at the level of 5% (P= < 0.05), *d* = net increase in water intake in dexamethasone and control groups between day 7 and day 12; a= PC; b=0.5mg/kg; c=1mg/kg; d=2mg/kg; e=4mg/kg; f=8mg/kg; g=16mg/kg.

Figure 1A–C: Mean values of net reduction in food intake, body weight (*d*) and net increase in water intake in control and dexamethasone treatment groups on day 12.

87.9% reduction in food intake in rats from day 7 to day 11. The high doses (8 mg, 16 mg/kg) caused a significant reduction in food intake compared to low (0.5 mg/kg and 1 mg/kg) and intermediate doses (2 mg/kg and 4 mg/kg) ($p<0.05$) However, the difference was insignificant between 8 mg/kg and 16 mg/kg of dexamethasone ($p>0.05$) (Figure 1B). A maximum of [25.1±2.0 ml] 67% and [16.5±2.8 ml] 65% rise in water intake was recorded in 16 mg/kg and 8 mg/kg dexamethasone respectively from day 7 to day 12 which were statistically significant compared to other doses of dexamethasone-treated groups ($p<0.05$) (Figure 1C).

Dose-dependent effects on fasting glucose and insulin in dexamethasone-treated groups

The dose-dependent hyperglycemia and hyperinsulinemia were observed with graded doses of dexamethasone (Graphs 1 and 2). The peak blood glucose (268.1 mg/dl, 270.6 mg/dl) and insulin levels (20.2 ng/ml and 19.4 ng/ml) were recorded in 8 mg/kg and 16 mg/kg dexamethasone groups, respectively, and the mean difference between them was statistically insignificant ($p>0.05$), whereas the difference in mean values of serum glucose and insulin levels between high and intermediate to low doses were statistically significant ($p<0.05$).

Post-IPGTT blood glucose levels in control and dexamethasone treatment groups on day 12

The maximum rise in serum glucose and insulin levels at 30, 60, 120 minutes of post-IPGGT were noted with high doses of dexamethasone treatment and the mean difference in the rise of serum glucose levels were significant compared to PC and low doses of dexamethasone ($p<0.05$) but not with intermediate doses ($p>0.05$) (Figure 2).

Determination of surrogate indices for the assessment of insulin sensitivity and insulin resistance and AGI

The dose-dependent effect of dexamethasone on surrogate indices for insulin resistance and sensitivity was determined by using serum glucose and insulin levels. The marked effects were noted with a high dose of 8 mg/kg treatment followed by 16 mg/kg compared to control, low, and intermediate-dose levels, they significantly raised the HOMA-IR and decreased HOMA-IS ($p<0.05$). Gutt and Matsuda's indices were noted significantly less compared to low and intermediate dose levels ($p<0.05$) (Figure 3A–D). The AGI was also significantly increased with high doses than with intermediate and low doses of dexamethasone ($p<0.05$) (Figure 3E).

Effect of graded doses of dexamethasone on serum lipids, creatinine

Dexamethasone produced dose-dependent increment in LDL, VLDL, TG, CH and markedly decreased the HDL levels compared to control ($p<0.05$). The maximum reduction in HDL and elevation of other lipoproteins was observed with 8 mg/kg and 16 mg/kg dexamethasone treatments and the difference was statistically significant compared to low and intermediate doses of dexamethasone ($p<0.05$) (Figure 4A–E). The serum creatinine was also significantly elevated with 8 mg/kg and 16 mg/kg treatment compared to low and intermediate doses of dexamethasone ($p<0.05$) (Figure 4F).

Dose-dependent effect of dexamethasone on urine glucose and ketones

Mild and moderate glycosuria and ketonuria were observed with 2 mg/kg and 4 mg/kg dexamethasone treatment respectively whereas, high doses of dexamethasone (8 mg/kg, 16 mg/kg) produced severe glycosuria and ketonuria-(Table 2).

Discussion

Dexamethasone, a glucocorticoid of intermediate action, is in use for many years in the management of many inflammations, immune-mediated and autoimmune conditions,

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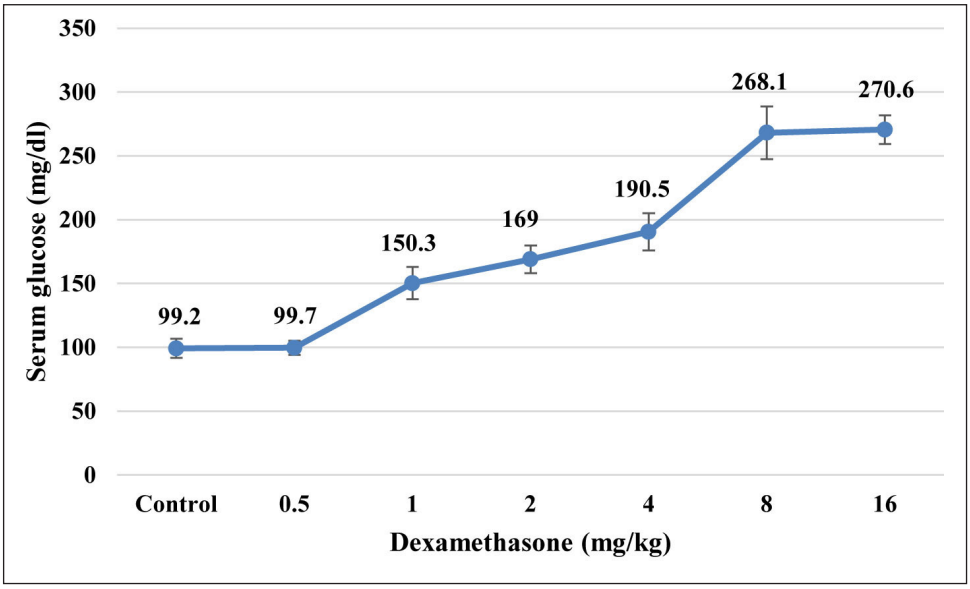
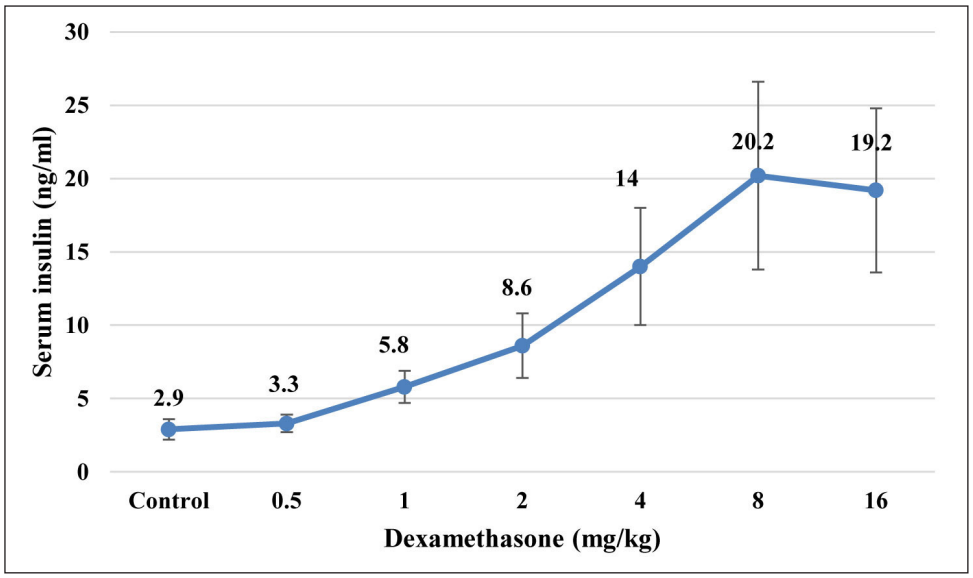


Graph 1: Effect of graded doses of dexamethasone (mg/kg BW) on fasting serum glucose in control and dexamethasone treatment groups on day 12.



Graph 2: Effect of graded doses of dexamethasone (mg/kg BW) on fasting serum insulin in control and dexamethasone treatment groups on day 12.

etc. However, it also has its own set of harmful effects on long-term use or the use of high doses, likely to be affecting metabolic and immune-mediated events in the body. Formerly, many investigators who used dexamethasone for the induction of insulin resistance in animals and succeeded [13] but outcomes were uncertain. Currently, the area of interest is to determine the dose of dexamethasone that causes maximum insulin resistance and its metabolic consequences.

In the present study, graded doses of dexamethasone have been administered to monitor the metabolic effects like hyperinsulinemia, hyperglycemia, and altered lipid profile and to obtain the optimal dose level which can cause significant insulin resistance to screen potential insulin sensitizers. In a 6-day study period, rats were administered with dexamethasone, as graded log doses starting from the minimum dose of 0.5 mg and extended up to a maximum of 16 mg per kg BW/day.

Regular and long-term use of glucocorticoids like dexamethasone is known to cause an increase in body weight, food intake (polyphagia) [14] and increased water intake [15], and excessive release of endogenous cortisol results in Cushing

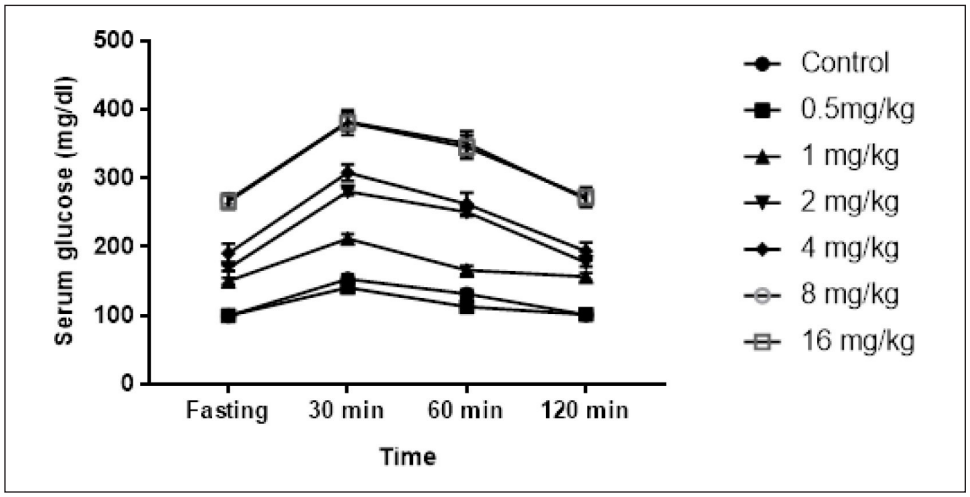


Figure 2: Mean values of post IPGTT serum glucose values in control and dexamethasone treatment groups on day 12.

Table 2: Mean values of urine glucose and ketones in control and dexamethasone treatment groups on day 12.

Group	Glycosuria	Ketonuria
I–Control	-	-
II–0.5 mg/kg	-	-
III–1 mg/kg	-	-
IV–2 mg/kg	+	-
V–4 mg/kg	++	++
VI–8 mg/kg	+++	+++
VII–16 mg/kg	+++	+++

Note: + Mild, ++ Moderate, +++ Severe, - Absent.

syndrome. In the current study, acute treatment (6 days) with high doses of (8 mg/kg and 16 mg/kg/day) dexamethasone for 6 days resulted in severe weight loss and reduced food intake which disagrees with the above-mentioned statements. A study which is in accordance with the current study results states that 10 µg/day dexamethasone caused weight reduction by 10 g/week. A theory was proposed in favor of the current findings on body weight loss is that the dexamethasone caused time and dose-dependent loss in body weight and muscle of rats due to up-regulation of a protein by name intramuscular myostatin and concentrations of mRNA, also associated with a fall in the expression of MCHII and these changes might occur through glucocorticoid receptor-mediated pathway [16]. The dexamethasone caused a dose-dependent reduction in food intake. Glucocorticoids inhibit leptin effects and maintain food intake whereas, higher glucocorticoid levels defend lipid stores in the body. This indicates that maintenance of appropriate levels of glucocorticoid would preserve the regular pattern of food intake and higher levels increase lipids and fat which supports the findings of the present study [17]. In rats, hypothalamic NPR-A (natriuretic peptide A) activation inhibits its water intake induced by dehydration upon chronic administration of glucocorticoids [18]. In the present study, polydipsia (increased water intake) was observed in a dose-dependent pattern with the administration of dexamethasone for a period of 6 days). This finding is in accordance with the above statement.

The dose-dependent effect of dexamethasone on serum glucose and insulin was postulated by plotting a dose-response curve for serum glucose and insulin. Peak concentrations of serum insulin and serum glucose were recorded with high doses of dexamethasone (8 mg/kg and 16 mg/kg/day) for 6 days. Previously few authors have been postulated that dexamethasone-induced hyperinsulinemia and hyperglycemia but there was wide variability in the dose and duration of the treatment [19, 20]. A conflict was found by Girish et al., a single dose of 1 mg/kg/ip dexamethasone did not decrease insulin sensitivity [21]. The reason might be that the dose and duration of dexamethasone given was might not sufficient to induce insulin resistance. A study by Matsumoto K et al. demonstrated that a decline in glucose disappearance against the high dose

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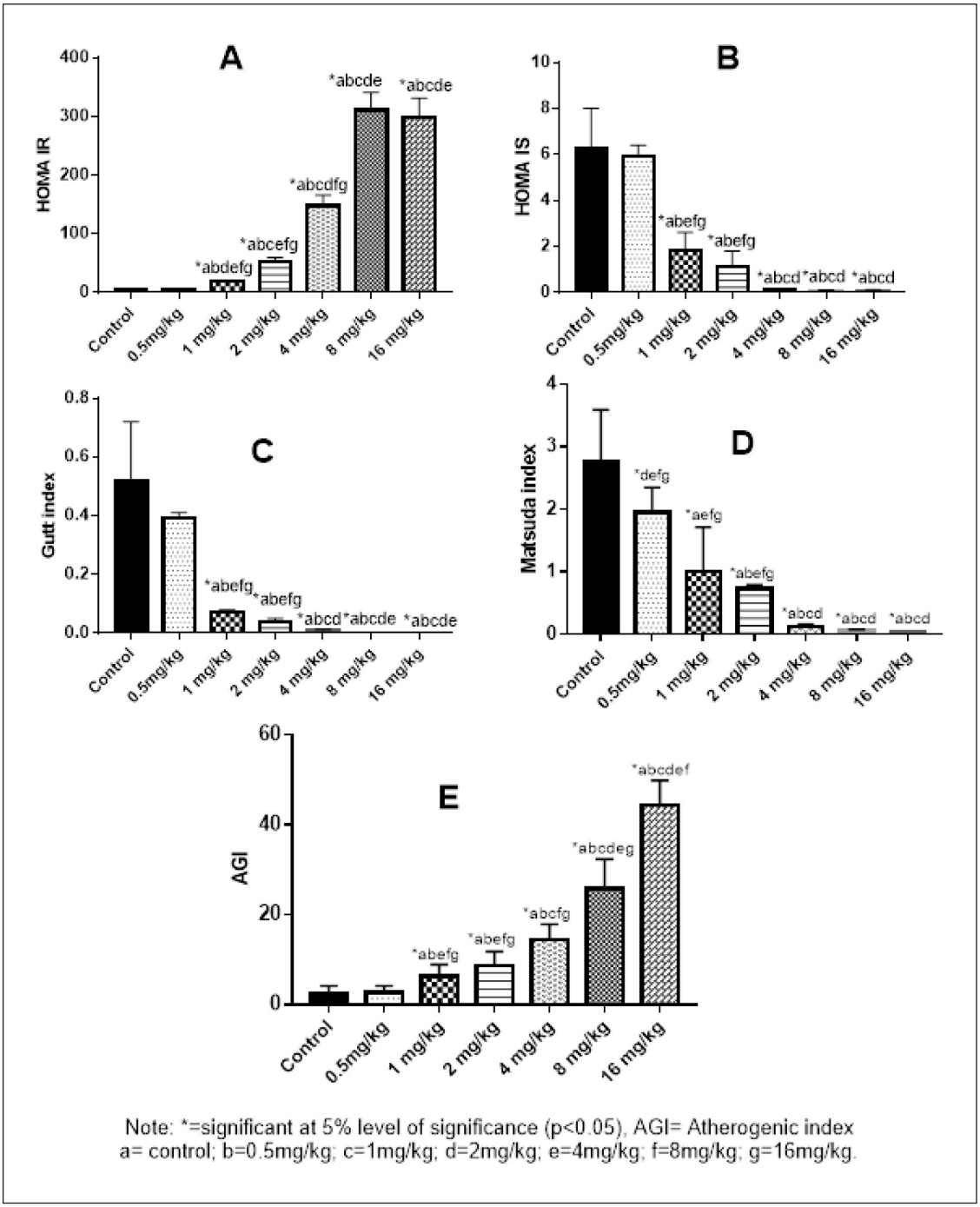

Figure 3A–E: Mean values of surrogate indices of insulin resistance and sensitivity in control and dexamethasone treatment groups on day 12.

of dexamethasone (6 mg/day) for 3 days might be associated with compensatory failure in the number of pancreatic beta cells [22]. Findings in the present study agree with the aforementioned theory, as the 8 mg/kg of dexamethasone continued a sustained rise in serum glucose levels above the level of 8 mg/kg but not the serum insulin level as it is declined just below with 16 mg/kg/day.

Higher doses of dexamethasone produced maximum glucose intolerance as evidenced by the rise in post-IPGTT glucose levels in Wistar rats and these findings were followed the study done by Rafacho A et al. [23, 24].

Sensitivity indices were severely disturbed with high doses of dexamethasone. Marked and sustained rise of HOMA-IR and fall

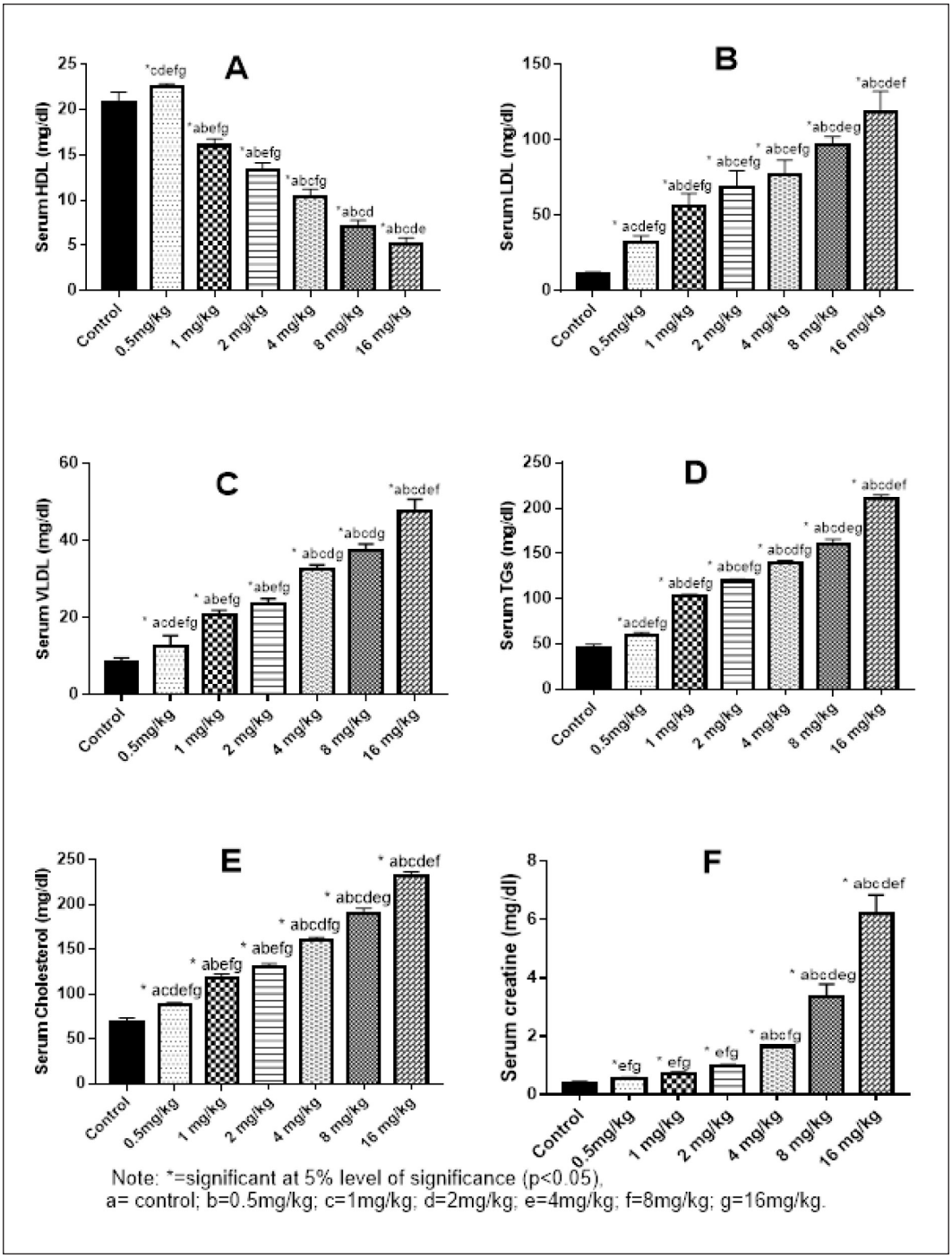

Figure 4A–F: Mean values of serum lipids and creatinine in control and dexamethasone treatment groups on day 12.

of HOMA-IS suggest that the hepatic component of insulin sensitivity was severely dampened, whereas the fall in Gutt index reveals the strong inhibitory action of dexamethasone on peripheral insulin sensitivity. Intense curtailment of insulin sensitivity in both hepatic and peripheral components was substantiated by declined Matsuda index.

The intention to determine the serum lipid profile was the insulin resistance and hyperinsulinemia typically associated with atherogenic dyslipidemia, which in turn increase the risk of atherogenic diseases [25]. The hyperinsulinemia intensifies the VLDL synthesis further into hypertriglyceridemia; VLDL undergoes a process of the progressive elimination of apolipoproteins

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from them that result in the formation of IDL and LDL [26]. Further, the pluripotent mesenchymal cell line from mouse bone marrow stroma differentiated into adipocytes with the treatment with 10^{-9}, $10^{-8,}$ and 10^{-7} molar concentrations of dexamethasone. They increased the number of TGs in the cells and expressed the fat cell-specific gene, 422(aP2), strongly raised with chronic exposure to the high concentration of dexamethasone [27]. This statement is in accordance with the present findings regarding lipid profile. Along with the dose-dependent rise in TGs, dexamethasone treatment also caused marked elevation of other lipoproteins as well. Nevertheless, the rise in levels of lipoproteins LDL, VLDL, CH, TGs were observed from 0.5 mg/kg itself, and the degree of rising continued until the 16 mg/kg dose. In contrast, the dose-dependent reduction in HDL levels began from a 1 mg/kg dose of dexamethasone treatment and a variable degree of reduction continued until the dose of 16 mg/kg.

The atherogenic index is an important surrogate predictor for hyperinsulinemia in men and with high CRP levels in women, which causes coronary heart disease and type II diabetes [28]. The maximum elevation of AGI was noted with high doses of dexamethasone treatment. The cause for this rise is possibly associated with profoundly declined HDL and elevated free cholesterol levels.

It is known that creatinine is a metabolic by-product of muscle catabolism and since dexamethasone causes enhancement in muscle catabolism and induces cachexia [29] which in turn results in elevated creatinine levels and this finding is the important reason for the reduction in body weight in the animal treated with dexamethasone.

The studies on dexamethasone-induced insulin resistance explained the signs of hyperglycemia and altered lipid profiles but none postulated glycosuria, an important sign of diabetes mellitus. The present study evaluated that, the low doses of dexamethasone (0.5 mg/kg and 1 mg/kg) did not cause glycosuria and ketonuria. However, the signs were observed from 1 mg/kg/day and maximum glycosuria and ketonuria were recorded in high doses of dexamethasone 8 mg/kg/day and 16 mg/kg/day. It is suggestive that, low doses of dexamethasone may not be sufficient to produce marked hyperglycemia, which would result in glycosuria and further into ketonuria. Maximum ketonuria was noted with 8 mg/kg/day and 16 mg/kg/day. This study strengthened the hypothesis that high doses of dexamethasone not only cause maximum insulin resistance but also induce glucose toxicity in Wistar rats.

Conclusion

Treatment with a high dose (8 mg/kg or 16 mg/kg) of dexamethasone for short-term (6 days) produced maximum hyperglycemia, hyperinsulinemia, and severe dyslipidemia, which are the key signs of insulin resistance. Administration of 8 mg/kg dexamethasone for 6 days would be sufficient for the induction of maximum insulin resistance in Wistar rats, and this model could be employed to screen potential insulin sensitizers.

Limitations

The rats in groups from 4 mg/kg onwards exhibited sluggish activity from day 3, and a temperature rise was noted in two rats in the 16 mg/kg group on day 6.

References

1. Andrews, R. C., Walker, B. R. (1999), Glucocorticoids and insulin resistance: old hormones, new targets. *Clin Sci*. 96(5): 513–523.
2. Lee, L., Sanders, R. A. (2012). Metabolic syndrome. *Pediatr Rev*. 33(10):459. https://doi.org/10.1542/pir.2014-0095.
3. Gounarides, J. S., Korach-Andre, M., Killary, K., Argentieri, G., Turner, O., Laurent, D. (2008). Effect of dexamethasone on glucose tolerance and fat metabolism in a diet-induced obesity mouse model. *Endocrinol*. 149(2):758–766.
4. Ai, J., Wang, N., Yang, M., Du, Z. M., Zhang, Y. C., Yang, B. F. Development of Wistar rat model of insulin resistance. *WJG* 11(24):3675.
5. Ghamarian, A., Abdollahi, M., Su, X., Amiri, A., Ahadi, A., Nowrouzi, A. (2012). Effect of chicory seed extract on glucose tolerance test (GTT) and metabolic profile in early and late-stage diabetic rats. *DARU J Pharmaceu Sci*. 20(1):1–9.
6. Kumar, S. S., Mukkadan, J. K. (2013). Anti-diabetic effect of oral administration of cinnamon in wistar albino rats. *Br Med J*. 2(3):97–99.
7. Hofmann, S. M., Dong, H. J., Li, Z., et al. (2002). Improved insulin sensitivity is associated with restricted intake of dietary

glycoxidation products in the db/db mouse. *Diabetes*. 51(7):2082–2089.
8. Aref, A. B. M., Ahmed, O. M., Ali, L. A., Semmler, M. (2013). Maternal rat diabetes mellitus deleteriously affects insulin sensitivity and beta-cell function in the offspring. *J Diab Res*. 2013:1–10. https://doi.org/10.1155/2013/429154.
9. Gutt, M., Davis, C. L., Spitzer, S. B., et al. (2000). Validation of the insulin sensitivity index (ISI0, 120): comparison with other measures. *Diab Res Clin Prac*. 47(3):177–184.
10. Mari, A., Pacini, G., Murphy, E., Ludvik, B., Nolan, J. J. (2001). A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. *Diabet Care* 24(3):539–548. https://doi.org/10.2337/diacare.24.3.539.
11. Hassan, S., Abd El-Twab, S., Hetta, M., Mahmoud, B. (2011). Improvement of lipid profile and antioxidant of hypercholesterolemic albino rats by polysaccharides extracted from the green alga Ulva lactuca Linnaeus. *Saudi J Bio Sci*. 18(4):333–340.
12. Salkovic-Petrisic, M., Lackovic, Z., Hoyer, S., Riederer, P. (2005). Central administration of alloxan impairs glucose tolerance in rats. *J Neural Trans*. 112(10):1391–1395.
13. Sikarwar, M. S., Patil, M. B. (2010). Antidiabetic activity of *Pongamia pinnata* leaf extracts in alloxan-induced diabetic rats. *Int J Ayu Res*. 1(4):199.
14. Chung, Y. C., Tzeng, C. Y., Chen, Y. I., Chang, S. W., Hsu, T. H., Ho, W. J. (2018). Improving insulin resistance with *Antrodia cinnamomea* mycelium powder to induce a hypoglycemic effect in dexamethasone-induced insulin-resistant rats. *Mol Med Rep*. 17(2):3260–3266.
15. Dallman, M. F., La Fleur, S. E., Pecoraro, N. C., Gomez, F., Houshyar, H., Akana, S. F. (2004). Minireview: glucocorticoids—food intake, abdominal obesity, and wealthy nations in 2004. *Endocrinol*. 145(6):2633–2638.
16. Liu, C., Guan, J., Kang, Y., Xiu, H., Chen, Y., Deng, B., Liu, K. (2010). Inhibition of dehydration-induced water intake by glucocorticoids is associated with activation of hypothalamic natriuretic peptide receptor-A in rat. *PLoS One*. 5(12):e15607.
17. Ma, K., Mallidis, C., Bhasin, S., Mahabadi, V., Artaza, J., Gonzalez-Cadavid, N., Arias, J., Salehian, B. (2003). Glucocorticoid-induced skeletal muscle atrophy is associated with upregulation of myostatin gene expression. *Am J Physiol Endocrinol Metabol*. 285(2):E363–E371.
18. Solano, J. M., Jacobson, L. (1999). Glucocorticoids reverse leptin effects on food intake and body fat in mice without increasing NPY mRNA *Am J Physiol Endocrinol Metabol*. 277(4):E708–E716.
19. Severino, C., Brizzi, P., Solinas, A., Secchi, G., Maioli, M., Tonolo, G. (2002). Low-dose dexamethasone in the rat: a model to study insulin resistance. *Am J Physiol Endocrinol Metabol*. 283(2):E367–E373.
20. Barbera, M., Fierabracci, V., Novelli, M., Bombara, M., Masiello, P., Bergamini, E., De Tata, V. (2001). Dexamethasone-induced insulin resistance and pancreatic adaptive response in aging rats are not modified by oral vanadyl sulfate treatment. *Eur J Endocrinol*. 145(6):799–806.
21. Kewalramani, G., Puthanveetil, P., Kim, M. S., Wang, F., Lee, V., Hau, N. (2008). Acute dexamethasone-induced increase in cardiac lipoprotein lipase requires activation of both Akt and stress kinases. *Am J Physiol Endocrinol Metabol*. 295(1):E137–E147.
22. Matsumoto, K., Yamasaki, H., Akazawa, S., et al, (1996). High-dose but not low-dose dexamethasone impairs glucose tolerance by inducing compensatory failure of pancreatic beta-cells in normal men. *J Clin Endocrinol Metabol*. 81(7):2621–2626.
23. Rafacho, A., Quallio, S., Ribeiro, D. L., et al. (2010). The adaptive compensations in endocrine pancreas from glucocorticoid-treated rats are reversible after the interruption of treatment. *Acta physiologica*. 200(3):223–235.
24. Rafacho, A., Abrantes, J. L. F., Ribeiro, D. L., et al. (2011). Morphofunctional alterations in endocrine pancreas of short- and long-term dexamethasone-treated rats. *Horm Metab Res*. 43(4):275–281.
25. Kumar, V. H., Nagendra Nayak, I. M., Huilgol, S. V., Yendigeri, S. M., Narendar, K., Rajasekhar, C. H. (2015). Dose dependent hepatic and endothelial changes in rats treated with dexamethasone. *JCDR*. 9(5):FF08.
26. Becker, D. M., Chamberlain, B., Swank, R., et al. (1988). Relationship between corticosteroid exposure and plasma lipid levels in heart transplant recipients. *The Am J Med*. 85(5):632–638.
27. Onat, A., Can, G., Kaya, H., Hergenç, G. (2010). "Atherogenic index of plasma" (log10 triglyceride/high-density lipoprotein – cholesterol) predicts high blood pressure, diabetes, and vascular events. *J Clin Lip*. 4(2):89–98.
28. Risch, L., Herklotz, R., Blumberg, A., Huber, A. R. (2001). Effects of glucocorticoid immunosuppression on serum cystatin C concentrations in renal transplant patients. *Clin Chem*. 47(11):2055–2059. https://doi.org/10.1093/clinchem/47.11.2055.
29. Wang, R., Jiao, H., Zhao, J., Wang, X., Lin, H. (2016). Glucocorticoids enhance muscle proteolysis through a myostatin-dependent pathway at the early stage. *PloS One*. 11(5):e0156225. https://doi.org/10.1371/journal.pone.0156225.

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