International Journal of Diabetes in Developing Countries
https://doi.org/10.1007/s13410-019-00791-6

ORIGINAL ARTICLE

The role of osteocalcin in mechanism of Steroid induced diabetes mellitus

Holla Avinash[1] · Vidyasagar Sudha[1] · Bairy Laxminarayan[2] · B. Nandakrishna[1] · B. A. Shastry[1] · Kamath Asha[3] · Manjunath Hande[1] · Adiga Shalini[4]

Received: 28 May 2019 / Accepted: 26 December 2019

Abstract

Background Steroids induced diabetes (SID), may be due to either insulin resistance (IR) or beta cell dysfunction or combination of both. Several studies have established that these effects of steroids may be mediated by an osteoblast derived protein called osteocalcin (OC). However, this effect has been described only in diabetic patients and has not been studied in SID patients.

Aim and study design A prospective observational cohort study was designed to evaluate the correlation between serum OC level and blood glucose profile, in patients on steroids.

Results Out of a total of 88 subjects who were on steroid therapy, 42(47.7%) subjects had their blood sugar levels in the diabetic range. Based on the glycemic status, subjects were divided into three groups, namely, normoglycemic, pre-diabetes and diabetes. The patients who developed SID were older than normoglycemic (mean age 43.15 vs 39.27years). The age (r=-0.105 p=0.5), BMI (r=-0.3 p= 0.07) and abdominal obesity (r=-0.32 p=0.04) were negatively correlated with serum osteocalcin in diabetes group. Serum osteocalcin level decreased as dose of steroid increased in all three groups (normogylcemic r=-0.701 p=0.004 prediabetes r=-0.3 p=0.07 diabetes -0.362 p=0.04). Fasting plasma glucose (r=-0.319 p=0.04), Fasting insulin (r=-0.10 p=0.5) and IR (r=-0.194 p=0.212) were increased with decrease in OC in patients in diabetes group.

Conclusion Decrease in serum osteocalcin level with increase in glycemic parameters in steroid induced diabetes group, point to have a new role in mechanism of steroid induced diabetes. This may be a novel target to discover drugs that can maintain the OC levels so that the effect of steroids on blood sugar level can be minimised.

Keywords Steroid-induced diabetes · Insulin resistance · Serum osteocalcin · Fasting insulin

Introduction

Since their introduction in 1950, steroids are commonly used in the treatment of both acute and chronic illnesses owing to their anti-inflammatory effects. They have many side effects, common among them hyperglycemia. The hyperglycemic effect of the steroids is one of the limiting factors to their clinical use [1, 2]

Steroids increase glucose levels in the blood by elevating glucose production in the liver and inhibiting glucose reuptake into muscles due to their effect of increasing insulin resistance (IR). They also reduce the pancreatic beta cell secretion by inducing apoptosis of beta cells. Yet, the mechanism of steroid-induced diabetes may be more complex as evidenced by newer studies [3–6].

Several studies have established that there is an endocrine function of vitamin K-dependent osteoblast-derived noncollagenous protein osteocalcin, in the regulation of blood glucose homeostasis. Steroids decrease the level of osteocalcin, which in turn contributes to the IR [7]. In type 2 diabetic patients, it was observed that lower serum osteocalcin (OC) levels were associated with increase in fasting plasma glucose (FPG), fasting insulin, and IR. [4] OC levels inversely correlated with FPG [5]. However, this effect has been

✉ Vidyasagar Sudha
vsagar33@yahoo.com

[1] Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Udupi District Karnataka 576104, India

[2] Pharmacology RAK College of Medical Science, Ras Al Khaimah, UAE

[3] Department of Statistics, Prasanna School at Public Health, Manipal Academy of Higher Education, Manipal, India

[4] Department of Pharmacology Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Udupi District Karnataka 576104, India

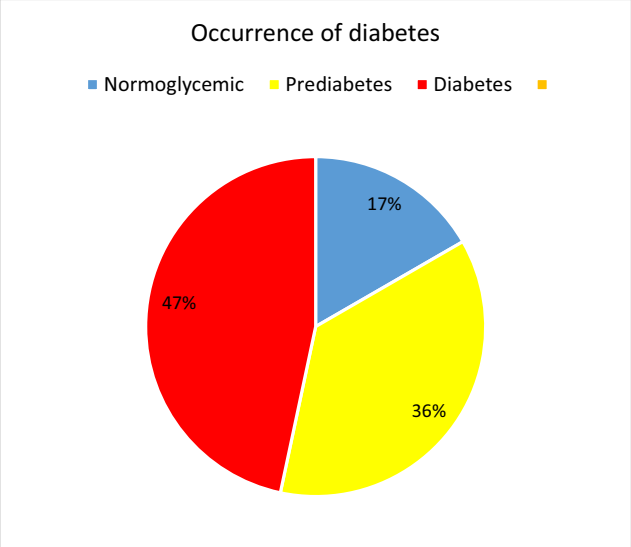


Fig. 1 Occurrence of diabetes after starting steroid therapy

described only in diabetic patients and has not been studied in steroid-induced diabetic (SID) patients. Hence, this prospective observational cohort study was designed to evaluate the correlation between serum osteocalcin level and blood glucose profile, in steroid therapy patients.

Methodology

This was a prospective observational, cohort study on nondiabetic subjects, aged between 18 and 70 years, on oral or parenteral steroid therapy for different diseases. A total of 317 patients were recruited from outpatients or inpatients in Kasturba Hospital Manipal, Karnataka from December 2015 to December 2017. Osteocalcin estimation was done in 88 patients and their data was analyzed.

Subjects who were on other drugs known to cause hyperglycemia, those who were already on steroid treatment before enrolment, those who were acutely ill, or having major organ dysfunction were excluded from the study. Osteoporosis subjects and pregnant women were also excluded.

Based on inclusion-exclusion criteria, informed consent was obtained from the patients. Detailed history of diabetes and comorbidities was recorded. All patients underwent basic anthropometry measurement including BMI and waist circumference.

In every case after detailed examination, FPG, postprandial glucose, glycated Hb, and serum osteocalcin were measured prior to starting steroids and were repeated in the first week (day 3/4) after starting steroid according to standard guidelines [8]..

The patients were divided into three groups following treatment based on ADA criteria for hyperglycemia into normoglycemic, prediabetic, and diabetic group [8].

Blood samples were collected after an overnight fasting in the morning for baseline measurement of FPG, fasting insulin, serum OC, and glycated Hb. Another sample was collected 2 h postprandial for measurement of postprandial glucose. Immediately after the collection of blood, samples were centrifuged. Analyses of FPG, glycated Hb, and postprandial glucose were done immediately. Serum samples for analysis of OC and fasting insulin were stored at – 80 °C. Same investigations were repeated except glycated Hb on 3rd or 4th day after steroid administration.

FPG and postprandial glucose (PPG) were measured by using automated auto analyzer Hitachi P800. The coefficient of variation was < 2% and < 5% for intra- and inter-batch, respectively; fasting insulin was assayed using insulin enzyme-linked immunosorbent assay kit manufactured by

Table 1 Demographic and clinical characteristics of patients across three groups ($N = 88$)

General and clinical characteristics		Normoglycemic ($n = 15$)	Prediabetic ($n = 31$)	Diabetic ($n = 42$)	p value
Age (years) (mean ± SD)		39.27 ± 12.09	43.43 ± 14.66	43.15 ± 14.67	0.6
Gender	Male (%) $n = 36$	6 (16.66)	13 (36.11)	17 (47.22)	0.44
	Female (%) $n = 52$	9 (17.3)	18 (34.6)	25 (48.07)	
Waist circumference (cm)	Male	90.56 ± 14.3	87 ± 7.19	87.17 ± 7.89	0.66
	Female	82.38 ± 7.78	87.40 ± 13.64	88.06 ± 5.86	0.18
BMI (kg/m^2)		23.68 ± 5.09	22.40 ± 4.67	25.49 ± 4.45	0.03*
Underlying disease[$]	Connective tissue and autoimmune disorder (%) $n = 57$	10 (17.5)	21 (36.8)	26 (45.61)	
	Lung diseases (%) $n = 31$	5 (16.1)	10 (32.2)	16 (51.6)	
Type of glucocorticoid used	Prednisolone (%) $n = 49$	12 (25.5)	18 (36.2)	19 (38.3)	
	Methylprednisolone (%) $n = 36$	3 (8.8)	11 (29.4)	22 (61.8)	
	Hydrocortisone (%) $n = 2$		2 (100)		
Dose of steroids(mg/kg)[#]		0.95 (0.77, 1.01)	0.97 (0.72, 2.49)	1.7 (0.94, 2.4)	0.1

*Statistically significant

[#] Median (Q1 Q3)

[$] Connective tissue and autoimmune disorder: *SLE*, systemic lupus erythematosus; *AIHA*, autoimmune hemolytic anemia; *RA*, rheumatoid arthritis; *ITP*, immune thrombocytopenic purpura

Lung disease: *ILD*, interstitial lung disease; *COPD*, chronic obstructive pulmonary disease; *BA*, bronchial asthma; sarcoidosis

Diagnostic Research Group (DRG) legal manufacturer Germany based on sandwich principle. The coefficient of variation was < 3% for intra- and inter-batch assay respectively. Serum osteocalcin levels were assayed using enzyme-linked immunosorbent assay kit manufactured by DIA source hOST-EASIA Kit Belgium with normal value of 5–25 ng/ml. Glycated Hb was measured by high-performance liquid chromatography method (HPLC) ion exchange-based method. IR was measured by HOMA 2 computerized method [9], which has been shown to correlate well with a euglycemic clamp for use in cross-sectional studies [10].

Statistical analyses

The occurrence of steroid-induced diabetes was calculated and presented in percentage. The continuous variables which were normally distributed were expressed as mean ± SD, and data which were not normally distributed were expressed as median and interquartile range. Categorical variables such as gender distribution and type of glucocorticoid were expressed in percentage. One-way ANNOVA test was used if the data was normally distributed. Kruskal Wallis test was used if data was not normally distributed. Wilcoxon signed rank test was used to compare baseline and posttreatment FPG, PPG, fasting insulin, IR, and osteocalcin concentration.

Spearman's rank correlation coefficient test was done to correlate the two continuous variables which were not normally distributed.

$p < 0.05$ was considered to be statistically significant. Statistical analysis was done by using SPSS software version 20.0.

Results

Out of 88 subjects, 42 (47%) subjects had their blood sugar in diabetic range and 31 (36%) subjects in prediabetic range after starting steroids and the remaining were normoglycemic as shown in Fig. 1.

Demographic and clinical characteristics of steroid-induced diabetes

The demographic and clinical characteristics of the study participants are presented in Table 1. Data is presented for all subjects ($n = 88$). Based on the glycemic status, subjects were divided into three groups, viz. normoglycemic, prediabetic, and diabetic. The patients who developed SID were older than normoglycemic (mean age 43.15 years vs 39.27 years) and similar to prediabetic group (mean age 43.43 years).The mean difference was not statistically significant across three groups. We did not find statistical significance in development of SID between male (47%) and female (48%). Mean waist circumference was not found to be statistically significant across

Table 2 Biochemical profile of patients across groups ($N = 88$)

Biochemical parameters	Normoglycemic ($n = 15$)			Prediabetic ($n = 31$)			Diabetic ($n = 42$)		
	Basal	Third day	*p* value	Basal	Third day	*p* value	Basal	Third day	*p* value
FPG (mg/dL)[$]	91 ± 10	92 ± 8	0.924	96 ± 12	110 ± 13	0.180	98 ± 21	127 ± 32	< 0.01*
PPG (mg/dL)[$]	118 ± 18	137 ± 19	0.62	114 ± 14	171 ± 49	< 0.01*	110 ± 14	213 ± 49	< 0.01*
Fasting insulin (μU/ml)[#]	7.82 (6.2, 26.3)	9.12 (6.8, 16.23)	0.765	10.2 (6.8, 16.9)	11.9 (8.8, 14.7)	0.165	12.02 (6.9, 20.9)	14.68 (9.5, 28.74)	0.137
IR[#]	1 (0.7, 3.6)	1 (0.9, 1.6)	0.3	1.5 (0.9, 2.6)	1.7 (1.1, 2.9)	0.08	1.5 (0.9, 2.5)	2.1 (1.2, 3.9)	0.08
Serum osteocalcin (ng/dL)[#]	7.7 (2.7, 10.37)	3.68 (0.7, 6.1)	0.04*	4.1 (3.29, 9.19)	1.81 (1.28, 3.67)	< 0.01*	5.27 (2.9, 8.22)	2.5 (1.14, 5.56)	< 0.01*

*Statistically significant

[#] Median (Q1 Q3)

[$] Mean ± standard deviation

FPG, fasting plasma glucose; *PPG*, postprandial glucose

Table 3 Correlation of serum osteocalcin levels with other parameters in steroid-induced diabetic patients

	Normoglycemic		Prediabetic		Diabetic	
	r value	*p* value	*r* value	*p* value	*r* value	*p* value
Age	− 0.002	0.99	− 0.26	0.15	− 0.105	0.53
BMI	− 0.018	0.99	0.126	0.5	− 0.3	0.07
Abdominal obesity	− 0.01	0.95	0.08	0.64	− 0.327	0.04*
Dose of steroids	− 0.701	0.004*	−0.3	0.07	− 0.362	0.02*
FPG	0.2	0.45	−0.18	0.31	− 0.319	0.04*
Fasting insulin	0.04	0.89	0.08	0.72	− 0.104	0.5
HOMA IR	0.05	0.88	0.277	0.14	− 0.194	0.212
HbA1c	0.178	0.6	− 0.25	0.2	0.01	0.82

r value: spearman correlation coefficient

*Statistically significant

BMI, body mass index; *FPG*, fasting plasma glucose; *HOMA IR*, homeostatic model assessment estimated IR; *HbA1c*, glycated hemoglobin

three groups. Mean difference of body mass index (BMI) was statistically significant between three groups and diabetic subjects had more BMI compared with prediabetic and normoglycemic group. The median prednisolone equivalent dose of steroid in diabetic group was higher: 1.7 (0.94, 2.4) compared with normoglycemic 0.95 (0.77, 1.01) and prediabetic 0.95 (0.72, 2.49). Fifty-seven patients had connective tissue and autoimmune disorder and 31 patients had lung diseases. Forty-nine patients were treated with prednisolone, 36 patients with methyl prednisolone, and 2 patients with hydrocortisone.

The biochemical parameters such as FPG, postprandial glucose, fasting insulin, and serum osteocalcin of the patients before and after steroid therapy are shown in Table 2**.** The mean FPG, PPG, and fasting insulin were increased in all three groups while serum osteocalcin was decreased after starting steroid therapy. We observed isolated PPG was increased in 24 (27.3%) subjects, isolated FPG was increased only in 8 subjects (9.1%), and both FPG and PPG were increased in 41 (45.5) subjects.

Correlation of serum osteocalcin with anthropometric measurement

We analyzed correlations between serum osteocalcin and anthropometric measurements including age, BMI, and abdominal obesity and various parameters related to glucose metabolism across three groups **(**Table 3). There is a weak negative correlation between serum osteocalcin and age in prediabetic and diabetic group and no correlation in normoglycemic group.

BMI and serum osteocalcin showed moderate negative correlation in diabetic group and weak positive correlation in prediabetic group and no correlation in normoglycemic group. Similarly, abdomen obesity and serum osteocalcin were significantly mild negatively correlated in diabetic group compared with weak positive correlation in prediabetic group and no correlation in normoglycemic group.

Dose of steroids was significantly negatively correlated with serum osteocalcin in all the three groups.

Subjects in prediabetic and diabetic group had serum osteocalcin reduced and FPG was increased. However, this was not seen in normoglycemic patients.

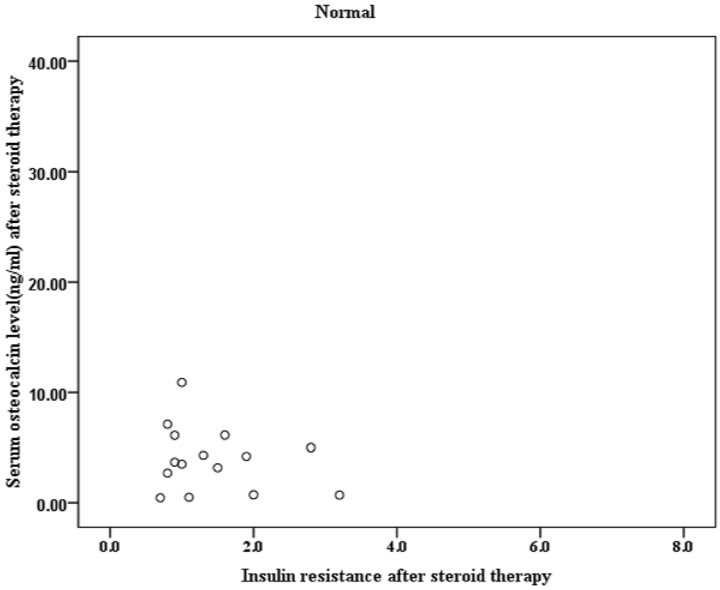
In diabetic group, fasting insulin and IR were weak negatively correlated with serum osteocalcin whereas no correlation was noticed in normoglycemic and mild positive in prediabetic group as shown in Fig. 2.

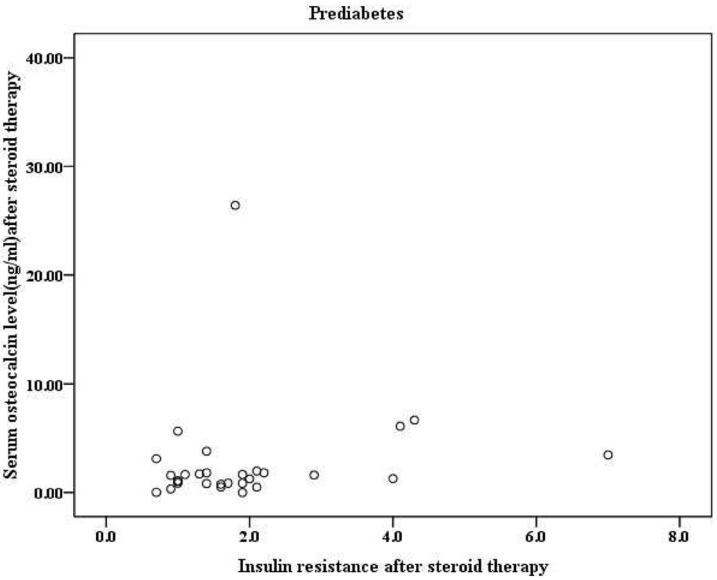
Discussion

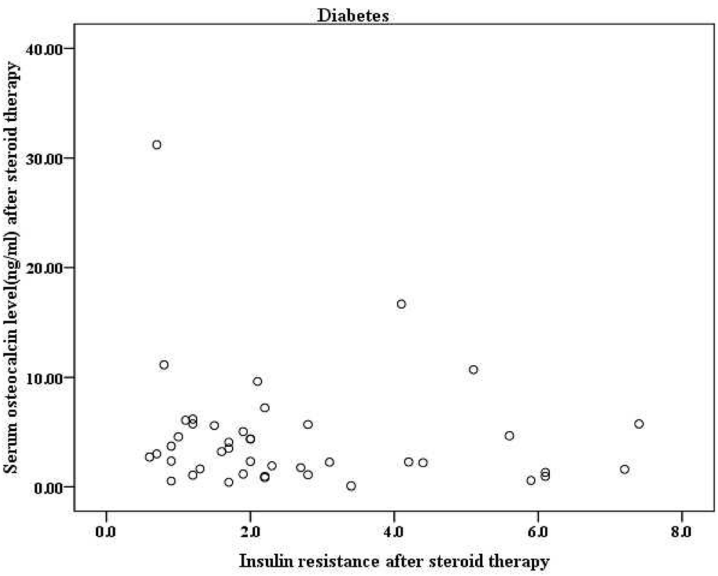
Hyperglycemia is a common side effect seen with steroid therapy. However, the mechanism underlying this is not well understood. Recently, many studies have explained that skeletal system is one of the insulin target tissues to regulate glucose homeostasis. In 2007, Karsentry laboratory observed that osteocalcin knockout mice were glucose intolerant and insulin resistant [11]. By these discoveries, we know that OC plays a central role in the pathogenesis of diabetes. Further in 2012, Brennan-Speranza and colleagues provided evidence that the osteoblast-derived peptide osteocalcin is one of the drivers of the metabolic derangements associated with glucocorticoid therapy [3].

The occurrence of diabetes in this study was found in 47% ($n = 42$) and occurrence of prediabetes or impaired glucose tolerance in 36% ($n = 31$). The occurrence of steroid-induced

Fig. 2 Scatter plot represents correlation of serum osteocalcin and IR across three groups. Scatter plot represents IR was weak negatively correlated ($r = -0.194$, $p = 0.212$) with serum osteocalcin in diabetic group whereas no correlation ($r = 0.05$ $p = 0.88$) was noticed in normoglycemic and mild positive ($r = 0.277$, $p = 0.14$) in prediabetic group


Normal
Serum osteocalcin level(ng/ml) after steroid therapy
40.00
30.00
20.00
10.00
0.00
0.0
2.0
4.0
6.0
8.0
Insulin resistance after steroid therapy


Prediabetes
Serum osteocalcin level(ng/ml)after steroid therapy
40.00
30.00
20.00
10.00
0.00
0.0
2.0
4.0
6.0
8.0
Insulin resistance after steroid therapy


Diabetes
Serum osteocalcin level(ng/ml) after steroid therapy
40.00
30.00
20.00
10.00
0.00
0.0
2.0
4.0
6.0
8.0
Insulin resistance after steroid therapy

diabetes differs across various studies from 1.5 to 47% [1]. The variability of this occurrence is due to the differences in patient population, different treatment protocols, and the definition of diabetes.

We observed 73% of subjects had increased in PPG with or without FPG compared with FPG in 54%. Normal or only mild elevation in fasting blood glucose and a large increase in postprandial glucose levels have been identified in various studies. The incidence of SID may be underestimated in studies which measured as only FPG and neglecting PPG, FPG rise is marginal [12, 13].In a study by Shanbhogue et al., it was observed that PPG increased in 89% whereas isolated FPG was raised only in 11% [14]. It has been further documented by Rao et al. that in 97% of the patients, PPG was raised with or without FPG. This makes the measurement of PPG a very important test for detecting SID [15].

Though several risk factors have been identified, these risk factors were not always constant across studies. Further, they seem to differ across different populations. These risk factors are quite unclear in Indians. [16]

In our study, patients who developed diabetes after steroid therapy were older compared with who did not develop diabetes (43.15 vs 39.27), and the same was observed in patients who has their blood sugar in prediabetic range (43.43 years). This is similar to Japanese study by Katsuyama et al. (65.2 vs 50.4) [16] and South Korean patients (65 vs 53) by Kim et al. [13] This may be due to a decrease in glucose tolerance with aging. Beta cell function also decreases with aging leading to decreased basal insulin level. In addition to these, factors such as decreased physical activity, obesity, and several medications will also increase IR in elderly.

The negative correlation between serum osteocalcin and the age and BMI of our subjects indicates that as age and BMI increase, the serum osteocalcin level decreases. Similar results were observed by Bao et al. in Chinese population [17] and Maddaloni et al. in type 1 diabetic patients [18]. However, this was different from the study by Kindbolm et al. where they observed a positive correlation with age and BMI in Swedish populations and no correlation with BMI was observed by Takashi et al. in Japanese patients [19, 20]

It is known that being overweight is often associated with impaired glucose tolerance and increased risk of developing type 2 diabetes. It is similar in our study that the group of subjects who developed diabetes following steroid therapy are overweight (mean BMI 25.49 kg/m^2) when compared with individuals who did not develop diabetes (mean BMI 23.68 kg/m^2).

Among the participants in our study, most of them are females**.** This was due to the fact that autoimmune disorders are seen most commonly in females and steroids are the primary drug of choice in most of the autoimmune disorders.

The median dose of steroids, taken by patients who developed diabetes (1.7 mg/kg prednisolone equivalent dose), was more compared with normoglycemics (0.95 mg/kg prednisolone dose) and prediabetic (0.97 mg/kg prednisolone dose). This is similar to other studies, by Donihi et al. [21] in western populations [21] and Rao et al. [15] in Indian patients.

In our study, we observed that low serum osteocalcin level was associated with increase in FPG, fasting insulin, and IR in diabetic group when compared with normoglycemic and prediabetic group. Similar studies on Caucasian and Asian populations [17, 22, 23] showed that OC levels negatively correlated with fasting blood glucose, fasting insulin, and IR in diabetic patients. However, several Chinese studies showed that OC was not related to IR [5, 21]. The reason behind IR caused by steroids was explained as chronic steroid treatment impairs insulin sensitivity in the liver, muscle, and adipose tissues. However, short-term steroid treatment decreases insulin sensitivity largely by reducing glucose disposal by muscle [24]. This loss of insulin sensitivity appears to be driven mainly by suppression of serum osteocalcin synthesis by steroids, providing a novel insight into the mechanism of steroid-induced diabetes mellitus [3, 25].

These findings have potentially important clinical implications, because for many diseases, glucocorticoids are still the first-line drug of choice. It is well known that steroids cause hyperglycemia. However, the mechanism of this is not clearly described. Since steroids suppress osteocalcin levels and decreased osteocalcin level causes IR, this may be one of the mechanisms for steroid-induced diabetes. This may be an important target for prevention of steroid-induced diabetes if future studies add to the validity of this hypothesis. Secondly, serum osteocalcin level and their correlation with glycemic patterns so far have been described only in diabetic patients. To the best of our knowledge, this may be the first study to see the correlation of serum osteocalcin levels and glycemic patterns in steroid therapy patients.

This study may have some limitations; we did osteocalcin levels on third day. Hence, we could not comment on the change in OC levels after first dose and interventional study design with measuring the osteocalcin in controlled environment would have made our study better. In the present study, many of the subjects developed hyperglycemia so there is lack of statistical power since the number of control was small.

Conclusion

As the therapeutic benefits of steroids continue to expand across medical specialties, the incidence of steroid-induced diabetes will continue to rise. Decrease in serum osteocalcin level with increase in glycemic parameters in steroid-induced diabetic group points to the new role in mechanism of steroid-induced diabetes. This may be a novel target to discover drugs that can maintain the OC levels so that the effect of steroids on blood sugar level can be minimized.

Funding information This study was financially supported by the Research Society for the study of diabetes in India (RSSDI) grants.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical clearance (IEC: 207/2015) was obtained from the Institutional Ethics Committee (IEC) of KMC and Hospital, Manipal.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Simmons LR, Molyneaux L, Yue DK, Chua EL. Steroid-induced diabetes: is it just unmasking of type 2 diabetes? ISRN Endocrinol. 2012:1–5.
2. Ha YJ, Lee KH, Jung SJ, Lee SW, Lee SK, Park YB. Glucocorticoid-induced diabetes mellitus in patients with systemic lupus erythematosus treated with high-dose glucocorticoid therapy. Lupus. 2011;20(10):1027–34.
3. Brennan-Speranza TC, Henneicke H, Gasparini SJ, Blankenstein KI, Heinevetter U, Cogger VC, et al. Osteoblasts mediate the adverse effects of glucocorticoids on fuel metabolism. J Clin Invest. 2012;122(11):4172–89.
4. Sarkar PD, Choudhury AB. Relationships between serum osteocalcin levels versus blood glucose, insulin resistance and markers of systemic inflammation in central Indian type 2 diabetic patients. Eur Rev Med Pharmacol Sci. 2013;17(12):1631–5.
5. Wang Q, Zhang B, Xu Y, Xu H, Zhang N. The relationship between serum osteocalcin concentration and glucose metabolism in patients with type 2 diabetes mellitus. Int J Endocrinol. 2013:1–7.
6. Wei J, Hanna T, Suda N, Karsenty G, Ducy P. Osteocalcin promotes β-cell proliferation during development and adulthood through Gprc6a. Diabetes. 2014;63(3):1021–31.
7. Ferris HA, Kahn CR. New mechanisms of glucocorticoid-induced insulin resistance: make no bones about it. J Clin Invest. 2012;122(11):3854–7.
8. Association AD. Standards of medical care in diabetes—2015 abridged for primary care providers. Clin Diabetes Publ Am Diabetes Assoc. 2015;33(2):97.
9. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412–9.
10. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004;27(6):1487–95.
11. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, et al. Endocrine regulation of energy metabolism by the skeleton. Cell. 2007;130(3):456–69.
12. Gonzalez-Gonzalez JG, Mireles-Zavala LG, Rodriguez-Gutierrez R, Gomez-Almaguer D, Lavalle-Gonzalez FJ, Tamez-Perez HE, et al. Hyperglycemia related to high-dose glucocorticoid use in noncritically ill patients. Diabetol Metab Syndr. 2013;5(1):1–18.
13. Kim SY, Yoo C-G, Lee CT, Chung HS, Kim YW, Han SK, et al. Incidence and risk factors of steroid-induced diabetes in patients with respiratory disease. J Korean Med Sci. 2011;26(2):264–7.
14. Shanbhogue VV, Vidyasagar S, Madken M, Varma M, Prashant CK, Seth P, et al. Indian diabetic risk score and its utility in steroid induced diabetes. J Assoc Physicians India. 2010;58(3):201–2.
15. Rao NK, Patil N, Vidyasagar S, Rau NR, Holla AM, Avinash A. Clinical and biochemical profile of steroid-induced diabetes. Asian J Pharm Clin Res. 2016;9(2):262–6.
16. Katsuyama T, Sada K-E, Namba S, Watanabe H, Katsuyama E, Yamanari T, et al. Risk factors for the development of glucocorticoid-induced diabetes mellitus. Diabetes Res Clin Pract. 2015;108(2):273–9.
17. Bao Y, Ma X, Yang R, Wang F, Hao Y, Dou J, et al. Inverse relationship between serum osteocalcin levels and visceral fat area in Chinese men. J Clin Endocrinol Metab. 2013;98(1):345–51.
18. Maddaloni E, D'Onofrio L, Lauria A, Maurizi AR, Strollo R, Palermo A, et al. Osteocalcin levels are inversely associated with Hba1c and BMI in adult subjects with long-standing type 1 diabetes. J Endocrinol Investig. 2014;37(7):661–6.
19. Kindblom JM, Ohlsson C, Ljunggren Ö, Karlsson MK, Tivesten A, Smith U, et al. Plasma osteocalcin is inversely related to fat mass and plasma glucose in elderly Swedish men. J Bone Miner Res. 2009;24(5):785–91.
20. Takashi Y, Koga M, Matsuzawa Y, Saito J, Omura M, Nishikawa T. Undercarboxylated osteocalcin can predict insulin secretion ability in type 2 diabetes. J Diabetes Investig. 2017;8(4):471–4.
21. Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA. Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. Endocr Pract. 2006;12(4):358–62.
22. Yeap BB, Chubb SP, Flicker L, McCaul KA, Ebeling PR, Beilby JP, et al. Reduced serum total osteocalcin is associated with metabolic syndrome in older men via waist circumference, hyperglycemia, and triglyceride levels. Eur J Endocrinol. 2011;164(2):315.
23. Zhou M, Ma X, Li H, Pan X, Tang J, Gao Y, et al. Serum osteocalcin concentrations in relation to glucose and lipid metabolism in Chinese individuals. Eur J Endocrinol. 2009;161(5):723–9.
24. Geer EB, Islam J, Buettner C. Mechanisms of glucocorticoid-induced insulin resistance: focus on adipose tissue function and lipid metabolism. Endocrinol Metab Clin. 2014;43(1):75–102.
25. Parker L, Lin X, Garnham A, McConell G, Stepto NK, Hare DL, et al. Glucocorticoid-induced insulin resistance in men is associated with suppressed undercarboxylated osteocalcin. J Bone Miner Res. 2019;34(1):49–58.