



# Effect of vitamin D supplement therapy on HbA1C and IGF-1 levels in children with type 1 diabetes mellitus and vitamin D deficiency

Elham Hashemi Dehkordi<sup>1</sup>, Vida Hashemi Dehkordi<sup>2</sup>, Saied Mohammad Reza Fatemi<sup>3</sup>, Mohammad Zolfaghari<sup>4</sup>

## ABSTRACT

**Background:** Studies indicated higher rate of vitamin D deficiency in Iranian children and also its potential role in both pathogenesis and management of Type 1 diabetes mellitus (T1DM), so we aimed to evaluate the impact of vitamin D supplement therapy on glycemic control and level of Insulin-like growth factor-I (IGF-1) in children with T1DM.

**Methods:** In this cross-sectional study, a total of 30 children with T1DM and serum 25-hydroxyvitamin D levels lower than 29 ng/ml were enrolled. In addition to insulin therapy, the patients underwent treatment with 50,000 units of cholecalciferol (vitamin D<sub>3</sub>) once a week for a period of 12 weeks. Mean of serum vitamin D, IGF-1 and hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), before and after treatment were compared.

**Results:** Serum vitamin D increased significantly after 12 weeks treatment ( $P < 0.001$ ). Mean level of IGF-1 and HbA<sub>1c</sub> increased and decreased significantly after treatment with vitamin D supplement, respectively ( $P = 0.01$  and  $0.04$ ). There was a significant negative correlation between HbA<sub>1c</sub> and IGF-1 ( $r = -0.69$ ,  $P < 0.001$ ) and 25(OH) D ( $r = -0.40$ ,  $P = 0.05$ ), 12 weeks after treatment with Vitamin D<sub>3</sub> supplement.

**Conclusion:** Our results indicated that vitamin D treatment enhance level IGF-1 which was accompanied by decreased levels of HbA<sub>1c</sub> in patients with T1DM. So, developing a proper vitamin D treatment guideline specified in T1DM patients would result in better glycemic control and proper prevention of its related microvascular and macrovascular complication.

**Keywords:** diabetes mellitus type 1, Glycated Hemoglobin A, insulin-like growth factor-I, vitamin D

## INTRODUCTION

Type 1 diabetes mellitus (T1DM) is one of the most common endocrine disorders of pediatric population. Some epidemiologic studies revealed that the prevalence of T1DM in children aged under 15 years old is approximately 490000, from which 78000 new cases diagnosed annually as new cases of T1DM (1,2). The epidemiology of the disease is varied in different population and geographical regions, but recent evidences indicated that the incidence of T1DM had increasing trend during last decades (3,4).

T1DM is associated with different microvascular and macrovascular complications which consequently effect on the disease cost and patients well-being and quality of life (5). Evidences indicated that appropriate glycemic control would reduce the risk of T1DM related morbidity and mortality. There are also documents that in addition to patients' subjective care some factors and supplementation could improve glycemic control of diabetic patients (6,7).

One of the supplements which are suggested that could improve glycemic control is vitamin D (8,9). There are also evidences regarding the role of vitamin D in the pathogenesis of T1DM (10,11). Recent review studies indicated that vitamin D supplementation both in prenatal and postnatal periods reduce the risk of T1DM (12).

<sup>1</sup> Department of Pediatric Endocrinology, Child growth and Development Research Center, Research Institute for primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran.

<sup>2</sup> School of Medicine, Islamic Azad University of Najafabad, Isfahan, Iran.

<sup>3</sup> Department of Pediatric Islamic Azad University of Najafabad, Isfahan, Iran.

<sup>4</sup> Student Research Committee, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

**Correspondence:** Vida Hashemi Dehkordi

Department of Pediatric, Islamic Azad University of Najafabad, Daneshgah Blvd, Najafabad, Isfahan Province.

E-mail: [mhmzolfaghari89@ssu.ac.ir](mailto:mhmzolfaghari89@ssu.ac.ir)

Received: 27 Jan 2018, Accepted: 24 Apr 2018

© 2018 by the authors; licensee Modestum Ltd., UK. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>).

Electronic Journal of General Medicine

Some previous studies mainly among adult patients with T1DM demonstrated that vitamin D could improve glycemic control of the patients by reduction in glycosylated haemoglobin (HbA1c) (8,9,12). There are few studies in this field among pediatric population (13,14).

In addition to HbA1c which is an indicator of glucose homeostasis, there are also some other indicators such as Insulin-like growth factor-I (IGF-1). It is a peptide hormone that is similar to insulin regarding its function and structure. The interaction of IGF-1 and growth hormone (GH) with insulin hormone plays a key role in the regulation of glucose homeostasis (15,16). Several reports showed that recombinant IGF-1 administration in diabetic patients could significantly reduce the level of blood glucose and increase insulin sensitivity (17,18).

There are also evidences regarding the association between vitamin D and IGF-1 level (19). It is suggested that vitamin D could increase the level of IGF-1 and improve the regulation of glucose homeostasis.

Considering that vitamin D deficiency is an important health problem worldwide in children and adolescents and recent studies from Iran also indicated higher rate of vitamin D deficiency in this age group and also its potential role in both pathogenesis and management of T1DM, so we aimed to evaluate the impact of vitamin D supplement therapy on glycemic control and level of IGF-1, the factors which are associated with T1DM related complication, in children with T1DM.

## MATERIALS AND METHODS

In this cross-sectional study, children and adolescents with T1DM aged 5-15 years with 25-hydroxyvitamin D levels lower than 75nmol/L (29 ng/ml) that referred to the endocrine clinic of Imam Hussein Children's Hospital, the pediatrics referral hospital of Isfahan province, affiliated to Isfahan University of Medical Sciences, were enrolled.

The study was conducted from September 2015 to September 2016. Protocol of the study was reviewed by pediatrics review board and approved by regional ethics committee of Isfahan University of Medical Sciences. All participants signed written informed consent to confirm their agreement to participate in the research.

The patients were selected by random sampling method. Those with malabsorptive disorders were excluded. Using a questionnaire, the medical history of the patients, demographic and anthropometric characteristics (weight, height and BMI) as well as data about the duration of T1DM, presentation, treatment and glycemic control of the disease were recorded in the medical files of the patients. In addition to their routine insulin therapy, the patients underwent treatment with 50,000 units of cholecalciferol (vitamin D<sub>3</sub>) once a week for a period of 12 weeks. Before treatment with vitamin D, as a baseline, serum vitamin D, IGF-1 and HbA1c were measured in the selected patients. After the treatment period the patients referred to the clinic and the level of mentioned biochemical factors were measured also. Mean of serum vitamin D, IGF-1 and HbA1c, before and after treatment with vitamin D<sub>3</sub> were compared.

### Laboratory Measurements

Venous blood samples were obtained from all selected patients. Serum vitamin D was measured by radioimmunoassay ELISA (Immunodiagnostic System Limited, UK). HbA1c was measured by means of ion-exchange high performance liquid chromatography (Arkray, Adams Japan). IGF-1 was measured by radioimmunoassay (RIA) using Pars Azmoon commercial kits (Tehran, Iran).

### Statistical Analysis

All statistical analyses were performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used for assessment of normality of data distribution. Because the data were normally distributed, *t-test* was used to compare differences before and after receiving vitamin D<sub>3</sub>. Partial correlation analysis adjusted for age, BMI, diabetes duration and baseline concentrations serum of 25-hydroxyvitamin D, IGF-1 and HbA1c was used to reveal the relationship between variables.

## RESULTS

In this study 30 children and adolescents (15 girls and 15 boys) with type 1 diabetes mellitus were selected. Mean age and BMI of studied population were 10.85 (3.24) and 17.92 (3.49), respectively. Mean duration of diabetes was 3.05 (1.32) years. Mean level of serum vitamin D, IGF-1 and HbA1c at the baseline and 12 weeks after vitamin D supplement therapy are presented in **Table 1**.

**Table 1:** Mean (SD) level of serum vitamin D, IGF-1 and HbA1c at the baseline and 12 weeks after vitamin D supplement therapy in children and adolescents with type 1 diabetes mellitus

Variables	Baseline	12 weeks after treatment	p-value
IGF-1 (ng/ml)	245.57 (108.9)	264.46 (104.30)	0.018
25(OH) D (ng/ml)	16.27 (6.56)	40.80 (1.17)	0.000
HbA1c (%)	8.89 (1.39)	8.60 (1.23)	0.047

IGF-1: Insulin-like growth factor-I; 25(OH)D: 25-hydroxyvitamin D; HbA1c: glycated haemoglobin

**Table 2:** Partial correlation analysis between serum 25(OH) D (ng/ml), IGF-1 and HbA1c, 12 weeks after Vitamin D supplement therapy in children and adolescents with type 1 diabetes mellitus

Variables	25(OH) D (ng/ml)		IGF-1 (ng/ml)	
	r	p-value	r	p-value
25(OH) D (ng/ml)	-	-	-	-
IGF-1 (ng/ml)	0.33	0.09	-	-
HbA1c (%)	-0.40	0.05*	-0.69	<0.000**

IGF-1: Insulin-like growth factor-I; 25(OH) D: 25-hydroxyvitamin D; HbA1c: glycated haemoglobin

Serum vitamin D increased significantly after 12 weeks treatment ( $P < 0.001$ ). Mean level of IGF-1 and HbA1c increased and decreased significantly after treatment with vitamin D supplement, respectively ( $P = 0.01$  for IGF-1 and  $P = 0.04$  for HbA1c).

Results of Partial correlation analysis of variable are presented in **Table 2**. All variable in Partial correlation adjusting for age, BMI, diabetes duration and serum concentration of 25(OH) D, IGF-1 and HbA1c at the baseline. The results indicated that there was a significant negative correlation between HbA1c and IGF-1 ( $r = -0.69$ ,  $P < 0.001$ ) and 25(OH) D ( $r = -0.40$ ,  $P = 0.05$ ), 12 weeks after treatment with Vitamin D3 supplement.

## DISCUSSION

In this study, we investigated the outcome of vitamin D treatment on glycemic control and level of IGF-1 in type 1 diabetic patients with vitamin D deficiency. Our findings indicated that vitamin D treatment increase the level of vitamin D and IGF-1 and also improve the glycemic control of the patients. There was significant negative association between glycemic control of the patients evaluated by HbA1c and the level of IGF-1 and serum vitamin D.

There are growing evidences that vitamin D deficiency have important role both in pathogenesis and glycemic control of type 1 diabetes mellitus (9,10). Some previous studies demonstrated that vitamin D supplementation results in better glycemic and metabolic control in type 1 diabetic patients (13,14). On the other hand, reports from Iran indicated that glycemic control (based on mean HbA1c) was poor in Iranian children with T1DM (20). It seems that high prevalence rate of vitamin D deficiency among Iranian population could explain the above mentioned situation of Iranian T1DM patients. This study conducted to evaluate the effectiveness of vitamin D supplement in the glycemic control of children with T1DM.

Several studies worldwide have demonstrated that the level of vitamin D is low in type1 diabetic patients and prevalence of vitamin D deficiency is high in diabetic than non-diabetic patients. Reported rate for vitamin D deficiency ranged from 50-80% in different population (21-23).

As mentioned different studies from various regions have investigated the effectiveness of vitamin D supplement therapy on glycemic control and level of HbA1c in type 1 diabetic patients and almost all of them indicated that vitamin D could improve glycometabolic status.

Two studies from different cities of Iran by Mohammadian et al. (13) and Ordooei et al. (24) showed that vitamin D supplement with different dosage and treatment protocol could improve glycemic control of T1DM children and adolescents. The design of our study was similar to the two mentioned studies. Ordooei and colleagues reported that reduction of HbA1c level in this group of patients occurred without any changes in mean level of their insulin dose (24).

Studies from Saudi Arabia, Egypt, Germany and Italy also indicated that vitamin D supplement therapy could improve glycemic control in children and adolescent with T1DM (14, 25-27).

Nwosu et al. in the USA did not report such an effect on HbA1c after 3 months of vitamin D supplementation in T1DM patients with vitamin D deficiency (28). Bizzarri and colleagues, in the IMDIAB XIII study also did not found any protective effect of vitamin D supplement on glycemic control of newly diagnosed T1DM patients, 6, 12 and 24 months after therapy (29).

Our results were similar to those reported the positive effect of vitamin D in reduction of HbA1c level. The dose of vitamin D in above mentioned studies were not similar. It seems that the administrated vitamin D dose in each study was according to the lifestyle variables of each population such as clothing, the food choice, socio-economic status, outdoor activities as well as climate of each region.

Regarding the effectiveness of vitamin D supplement therapy on IGF-1 there were few studies in literature review. It is well known that IGF-1 can reduce hepatic glucose production and increase in peripheral glucose uptake (30). On the other hand, serum IGF-1 levels negatively correlated with HbA1c (31,32). Færch et al. demonstrated a significant negative association between IGF-1 and glycemic control of T1DM patients (33).

Evidences indicated that serum level of IGF-1 is reduced in newly diagnosed children with T1DM and insulin therapy increase the level of IGF-1 in these patients (34). Carroll et al. showed that IGF-1 replacement therapy could increase insulin sensitivity in adult patients with T1DM (35). Ameri et al. found that vitamin D supplement could increase the level of IGF-1 in adult population (36).

Thus, it is suggest that vitamin D supplement in addition to insulin therapy could increase the level of IGF-1 and consequently improve the glycemic control of patients with T1DM. The results of our study confirms the suggestion. There was a significant negative correlation between HbA1c and IGF-1 and vitamin D, 12 weeks after treatment with Vitamin D3 supplement. There was not similar study in this regard among pediatric population with T1DM, so it seems that further prospective studies with larger sample size should be designed for proving more accurate conclusion in this field.

The limitations of this study were the small sample size of the patients, its cross sectional design and short term follow up of the patients. It is recommended to design clinical trials with larger sample size including also those with normal level of vitamin D.

Evaluation of the effect of vitamin D therapy on serum level of IGF-1 is considered the strength of current study due to its novelty among pediatric T1DM patients.

## CONCLUSION

The results of this study indicated that vitamin D treatment enhance level IGF-1 which was accompanied by decreased levels of HbA1c in patients with T1DM. So, developing a proper vitamin D treatment guideline specified in T1DM patients would result in better glycemic control and proper prevention of its related microvascular and macrovascular complication.

## REFERENCES

1. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Cheng AY. Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction. *Can J Diabetes*. 2013;37 Suppl 1:S1-3.
2. Gan MJ, Albanese-O'Neill A, Haller MJ. Type 1 diabetes: current concepts in epidemiology, pathophysiology, clinical care, and research. *Curr Probl Pediatr Adolesc Health Care*. 2012;42(10):269-91. <https://doi.org/10.1016/j.cppeds.2012.07.002>
3. You WP, Henneberg M. Type 1 diabetes prevalence increasing globally and regionally: the role of natural selection and life expectancy at birth. *BMJ Open Diabetes Res Care*. 2016;4(1):e000161. <https://doi.org/10.1136/bmjdr-2015-000161>
4. Teeäär T, Liivak N, Heilman K, Kool P, Sor R, Paal M, Einberg U, Tillmann V. Increasing incidence of childhood-onset type 1 diabetes mellitus among Estonian children in 1999-2006. Time trend analysis 1983-2006. *Pediatr Diabetes*. 2010;11(2):107-10. <https://doi.org/10.1111/j.1399-5448.2009.00535.x>
5. Chawla A, Chawla R, Jaggi S. Microvascular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian J Endocrinol Metab*. 2016;20(4):546-51. <https://doi.org/10.4103/2230-8210.183480>
6. Gunasekara P, Hettiarachchi M, Liyanage C, Lekamwasam S. Effects of zinc and multimineral vitamin supplementation on glycemic and lipid control in adult diabetes. *Diabetes Metab Syndr Obes*. 2011;4:53-60.
7. Cazeau RM, Huang H, Bauer JA, Hoffman RP. Effect of Vitamins C and E on Endothelial Function in Type 1 Diabetes Mellitus. *J Diabetes Res*. 2016;2016:3271293. <https://doi.org/10.1155/2016/3271293>

8. George PS, Pearson ER, Witham MD. Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. *Diabet Med.* 2012;29(8):e142-50. <https://doi.org/10.1111/j.1464-5491.2012.03672.x>
9. Hutchinson MS, Figenschau Y, Njølstad I, Schirmer H, Jorde R. Serum 25-hydroxyvitamin D levels are inversely associated with glycated haemoglobin (HbA(1c)). The Tromsø Study. *Scand J Clin Lab Invest.* 2011;71(5):399-406. <https://doi.org/10.3109/00365513.2011.575235>
10. Todd JA. Etiology of type 1 diabetes. *Immunity.* 2010;32(4):457-67. <https://doi.org/10.1016/j.immuni.2010.04.001>
11. Penna-Martinez M, Badenhop K. Inherited Variation in Vitamin D Genes and Type 1 Diabetes Predisposition. *Genes (Basel).* 2017;8(4). pii: E125. <https://doi.org/10.3390/genes8040125>
12. Dong JY, Zhang WG, Chen JJ, Zhang ZL, Han SF, Qin LQ. Vitamin D intake and risk of type 1 diabetes: a meta-analysis of observational studies. *Nutrients.* 2013;5(9):3551-62. <https://doi.org/10.3390/nu5093551>
13. Mohammadian S, Fatahi N, Zaeri H, Vakili MA. Effect of vitamin d3 supplement in glycemic control of pediatrics with type 1 diabetes mellitus and vitamin d deficiency. *J Clin Diagn Res.* 2015;9(3):SC05-7. <https://doi.org/10.7860/JCDR/2015/10053.5683>
14. Aljabri KS, Bokhari SA, Khan MJ. Glycemic changes after vitamin D supplementation in patients with type 1 diabetes mellitus and vitamin D deficiency. *Ann Saudi Med.* 2010;30(6):454-8. <https://doi.org/10.4103/0256-4947.72265>
15. Clemmons DR. Metabolic actions of insulin-like growth factor-I in normal physiology and diabetes. *Endocrinol Metab Clin North Am.* 2012;41(2):425-43, vii-viii. <https://doi.org/10.1016/j.ecl.2012.04.017>
16. Holt RI, Simpson HL, Sönksen PH. The role of the growth hormone-insulin-like growth factor axis in glucose homeostasis. *Diabet Med.* 2003;20(1):3-15. <https://doi.org/10.1046/j.1464-5491.2003.00827.x>
17. Saukkonen T, Shojaee-Moradie F, Williams RM, Amin R, Yuen KC, Watts A, Acerini CL, Umpleby AM, Dunger DB. Effects of recombinant human IGF-1/IGF-binding protein-3 complex on glucose and glycerol metabolism in type 1 diabetes. *Diabetes.* 2006;55(8):2365-70. <https://doi.org/10.2337/db05-1646>
18. McDonald A, Williams RM, Regan FM, Semple RK, Dunger DB. IGF-1 treatment of insulin resistance. *Eur J Endocrinol.* 2007;157 Suppl 1:S51-6. <https://doi.org/10.1530/EJE-07-0271>
19. Bogazzi F, Rossi G, Lombardi M, Tomisti L, Sardella C, Manetti L, Curzio O, Marcocci C, Grasso L, Gasperi M, Martino E. Vitamin D status may contribute to serum insulin-like growth factor I concentrations in healthy subjects. *J Endocrinol Invest.* 2011;34(8):e200-3.
20. Setoodeh A, Mostafavi F, Hedayat T. Glycemic control in Iranian children with type 1 diabetes mellitus: effect of gender. *Indian J Pediatr.* 2012;79(7):896-900. <https://doi.org/10.1007/s12098-011-0613-8>
21. Bin-Abbas BS, Jabari MA, Issa SD, Al-Fares AH, Al-Muhsen S. Vitamin D levels in Saudi children with type 1 diabetes. *Saudi Med J.* 2011;32(6):589-92.
22. Greer RM, Portelli SL, Hung BS, Cleghorn GJ, McMahon SK, Batch JA, Conwell LS. Serum vitamin D levels are lower in Australian children and adolescents with type 1 diabetes than in children without diabetes. *Pediatr Diabetes.* 2013;14(1):31-41. <https://doi.org/10.1111/j.1399-5448.2012.00890.x>
23. Wierzbicka E, Szalecki M, Pludowski P, Jaworski M, Brzozowska A. Vitamin D status, body composition and glycemic control in Polish adolescents with type 1 diabetes. *Minerva Endocrinol.* 2016;41(4):445-55.
24. Ordooei M, Shojaoddiny-Ardekani A, Hoseinipoor SH, Miroliai M, Zare-Zardini H. Effect of vitamin D on HbA1c levels of children and adolescents with diabetes mellitus type 1. *Minerva Pediatr.* 2017;69(5):391-395.
25. Hafez M, Hassan M, Musa N, Abdel Atty S, Azim SA. Vitamin D status in Egyptian children with type 1 diabetes and the role of vitamin D replacement in glycemic control. *J Pediatr Endocrinol Metab.* 2017;30(4):389-394. <https://doi.org/10.1515/jpem-2016-0292>
26. Bogdanou D, Penna-Martinez M, Filmann N, Chung TL, Moran-Auth Y, Wehrle J, Cappel C, Huenecke S, Herrmann E, Koehl U, Badenhop K. T-lymphocyte and glycemic status after vitamin D treatment in type 1 diabetes: A randomized controlled trial with sequential crossover. *Diabetes Metab Res Rev.* 2017;33(3). <https://doi.org/10.1002/dmrr.2865>
27. Savastio S, Cadario F, Genoni G, Bellomo G, Bagnati M, Secco G, Picchi R, Giglione E, Bona G. Vitamin D Deficiency and Glycemic Status in Children and Adolescents with Type 1 Diabetes Mellitus. *PLoS One.* 2016;11(9):e0162554. <https://doi.org/10.1371/journal.pone.0162554>

28. Nwosu BU, Maranda L. The effects of vitamin D supplementation on hepatic dysfunction, vitamin D status, and glycemic control in children and adolescents with vitamin D deficiency and either type 1 or type 2 diabetes mellitus. *PLoS One*. 2014 Jun 11;9(6):e99646. <https://doi.org/10.1371/journal.pone.0099646>
29. Bizzarri C, Pitocco D, Napoli N, Di Stasio E, Maggi D, Manfrini S, Suraci C, Cavallo MG, Cappa M, Ghirlanda G, Pozzilli P. IMDIAB Group: No protective effect of calcitriol on beta-cell function in recent-onset type 1 diabetes: the IMDIAB XIII trial. *Diabetes Care*. 2010;33(9):1962-3. <https://doi.org/10.2337/dc10-0814>
30. Friedrich N, Thuesen B, Jørgensen T, Juul A, Spielhagen C, Wallaschofski H, Linneberg A. The association between IGF-1 and insulin resistance: a general population study in Danish adults. *Diabetes Care*. 2012;35(4):768-73. <https://doi.org/10.2337/dc11-1833>
31. Kabir G, Hossain M, Faruque MO, Hassan N, Hassan Z, Nahar Q, Shefin SM, Alauddin M, Ali L. Association of serum free IGF-1 and IGFBP-1 with insulin sensitivity in impaired glucose tolerance (IGT). *Int J Diabetes Mellit*. 2010;2(3):144-7. <https://doi.org/10.1016/j.ijdm.2010.09.003>
32. Simpson HL, Jackson NC, Shojaee-Moradie F, Jones RH, Russell-Jones DL, Sönksen PH, Dunger DB, Umpleby AM. Insulin-like growth factor I has a direct effect on glucose and protein metabolism, but no effect on lipid metabolism in type 1 diabetes. *J Clin Endocrinol Metab*. 2004;89(1):425-32. <https://doi.org/10.1210/jc.2003-031274>
33. Færch L, Juul A, Pedersen-Bjergaard U, Thorsteinsson B. Association of IGF1 with glycemic control and occurrence of severe hypoglycemia in patients with type 1 diabetes mellitus. *Endocrine Connections*. *Endocr Connect*. 2012;1(1):31-6. <https://doi.org/10.1530/EC-12-0012>
34. Shiva S, Behbod H, Ghergherechi R. Effect of insulin therapy on IGF-1 level in children with new-onset type 1 diabetes mellitus: a comparison between DKA and non-DKA. *J Pediatr Endocrinol Metab*. 2013;26(9-10):883-6. <https://doi.org/10.1515/jpem-2013-0057>
35. Carroll PV, Christ ER, Umpleby AM, Gowrie I, Jackson N, Bowes SB, Hovorka R, Croos P, Sönksen PH, Russell-Jones DL. IGF-1 treatment in adults with type 1 diabetes: effects on glucose and protein metabolism in the fasting state and during a hyper insulinemic-euglycemic amino acid clamp. *Diabetes*. 2000;49(5):789-96. <https://doi.org/10.2337/diabetes.49.5.789>
36. Ameri P, Giusti A, Boschetti M, Bovio M, Teti C, Leoncini G, Ferone D, Murialdo G, Minuto F. Vitamin D increases circulating IGF-1 in adults: potential implication for the treatment of GH deficiency. *Eur J Endocrinol*. 2013;169(6):767-72. <https://doi.org/10.1530/EJE-13-0510>



<http://www.ejgm.co.uk>