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Double-Blind Placebo-Controlled Effectiveness of Cholecalciferol (Vitamin D3) Plus Magnesium and Zinc in Management of Type 1 Diabetes (T1d) In Pediatric Age Group

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Abstract

Background: Vitamin D3 can adjust glycemic control and spot to their etiological factor on type 1 diabetes (T1D), increased transcription of insulin receptor genes by 1, 25 (OH) D. types 1 diabetes is associated with magnesium deficiency. Antibody against Zn-transport 8 has been well documented as a diagnostic consideration for T1D Objective: Evaluate efficacy of Vitamin D3 plus magnesium and zinc for tight glycemic control and decrement in symptoms and sign of type 1 diabetes (T1D) and/or diabetic ketoacidosis in pediatric age group. Patients and Methods: double-blind placebo-controlled Fifty patient type 1 diabetes (T1D) child under 16 years from outpatient clinic of pediatrics department in Tikrit teaching and /or salahaldeen teaching Hospital were collected and admitted as inpatient from 2 January 2012 to 2 June 2019. 25 Child ((vitamin D3 magnesium, zinc)) group were take regime as (800 IU/day of vitamin D3, Magnesium 3 mg/kg/d and zinc 2 mg per day) for 180 day, oral capsule prior to meal once daily. 25 Child were received (placebo capsule) as control group for 180 days. Both groups receive recommended dose of insulin twice daily. Results : The Decrement in rate, mean ± SD of symptoms and sign of type 1 diabetes (T1D) at 4 month of ((vitamin D3 magnesium, zinc)) group for Polydipsia11 9.5 (1.4), Glycosuria10 9.2(1.1), Hyperglycemia 108.2 (1.8), were significantly less than rate, mean ± SD of symptoms and sign of type 1 diabetes (T1D) at 4 month of Placebo group for Polydipsia23 20.0(2.5),Glycosuria 2119.52(1.48), Hyperglycemia 24 20.74 (3.26). The Decrement in rate, mean ± SD of Symptoms and sign of diabetic ketoacidosis at 4 month of ((vitamin D3 magnesium, zinc)) group for Acidotic breathing11 10.9(1.3),blood sugar <350 10 8.93 (2.3), Drowsiness11 9.9(1.1),coma12 10.8(1.2),were significantly less than rate , mean,SD of Symptoms and sign of diabetic ketoacidosis at 4 month of Placebo group for Acidotic breathing2422.7(2.25),blood sugar<350 2522.85 (2.15), Drowsiness 23 20.55 (2.45), coma 2420.74 (3.26) and other result can be seen in table 1-2.The Decrement in rate, mean ± SD of symptoms and sign of type 1 diabetes (T1D) at 8month of ((vitamin D3 magnesium, zinc))group for Polydipsia 5 3.2(1.8),Glycosuria5 4.0(1.0),Hyperglycemia64.9(1.3),glycosylated hemoglobin < 7 5 3.2(1.8),were significantly less than rate, mean ± SD of symptoms and sign of type 1 diabetes (T1D) at 8month of Placebo group for Polydipsia 25 22.55 (2.45), Glycosuria 23 20.5 (2.5) ,Hyperglycemia24 21.75(2.25),glycosylated hemoglobin < 7 25 22.65 (2.35). The Decrement in rate, mean ± SD of Symptoms and sign of diabetic ketoacidosis at 8 month of ((vitamin D3 magnesium, zinc)) group for severe dehydration 4 3.8 (0.2) , blood sugar <350 4 2.8 (1.2) , Drowsiness 42.7 (1.3), coma 2 1.7(0.3), were significantly less

Keyword: type 1 diabetes (T1D), Vitamin D3, pediatric group, magnesium, zinc

than rate, mean ± SD of Symptoms and sign of diabetic ketoacidosis at 8 month of Placebo group for Severe dehydration 21 18.22 (2.82), , blood sugar <350 25 22.85 (2.15) , Drowsiness 23 20.5 (2.5), coma 2420 74 (3.26) and other result can be seen in table 3-4. The 12 month mean±SD overall reduction in symptoms and sign of type 1 diabetes (T1D) of (Vitamin D3) plus magnesium and zinc group was (92.84%) (23.21 ±1.56) which is more than in Placebo group (14.56%) (3.64±2.19) (P= 0.01) Additionally, the 12 month mean±SD overall reduction in symptoms and sign of diabetic ketoacidosis of (Vitamin D3) plus magnesium and zinc group was (90.88%) (22.72±1. 40) which is more than in Placebo group (9.76%) (11.44±2.81) (P= 0.01). As in Table (5) & Figure (1).Conclusion: Cholecalciferol (Vitamin D3) plus magnesium and zinc can be safe and effective used for tight glycemic control and decrement in symptoms and sign of type 1 diabetes (T1D) and/or diabetic ketoacidosis in pediatric age group.

Introduction

Vitamin D3 can adjust glycemic control and spot to their etiological factor on type 1 diabetes **(**T1D**)** [(1)]. At the level of the pancreatic islets, $1,25(OH)_2D_3$ decreased in vivo[(2,3)] and in vitro proinflammatory chemokine and cytokine expression (e.g., IL6)[(4)].Vitamin D receptor in skeletal muscle[(5)] and suppression of renin gene, increased transcription of insulin receptor genes by 1,25(OH)D [(6)]. It is well known that type 1 diabetes is associated with magnesium deficiency, having 25% to 39% prevalence [(7)]. This deficit could be associated with the development of late diabetic complications, especially Microangiopathic [(8)]. Low levels of zinc in drinking water have been associated with high risk of type 1 diabetes [(9)]. The presence of an antibody against Zn-transport 8 has been well documented as a diagnostic consideration for T1D [(10)]

Aim of study

Evaluate efficacy of Cholecalciferol (Vitamin D3) plus magnesium and zinc for tight glycemic control and decrement in symptoms and sign of type 1 diabetes (T1D) and/or diabetic ketoacidosis in pediatric age group

Patients and Methods

All ethical and legal issues taken from families and acceptances from local health salahaldeen authority in written papers before starting the study

Case sample

According diagnostic criteria of type 1 diabetes **(**T1D**)** by the American Diabetes Association (ADA) [(11)].
double-blind placebo-controlled Fifty type 1 diabetes **(**T1D**)** child under 16 years from outpatient clinic of pediatrics department in Tikrit teaching and /or salahaldeen teaching Hospital were collected and admitted as inpatient from 2 January 2012 to 2 June 2019.
25 child type 1 diabetes **(**T1D**)** (Cholecalciferol (Vitamin D3) plus magnesium and zinc) group were instructed to take regime at time of admission and after discharge as (**800 IU/day of vitamin D_3**[(12)]**, Magnesium** 3 mg/kg/d[(13)] and **zinc** 2 mg [(14)] per day) **for 180 day**, oral capsule prior to meal once daily . 25 child type 1 diabetes **(**T1D**)** age- and sex-matched were received (placebo capsule) as control group for **180 day**. Both groups receive recommended dose of insulin (Mixtard 30:70) [(15)] Twice daily.
Follow-up every three week visit for 12 month to pediatrics outpatient's and /or inpatient of Tikrit teaching and / or salahaldeen teaching Hospital for review full questionnaire concerning update medical consultation plus ensure medication compliance were received.
A designed forma were use to collect information about compare effect of (Cholecalciferol (Vitamin D3) plus magnesium and zinc) group and placebo group on Signs and symptoms of type 1 diabetes as Polydipsia, nocturnal polyurea, Glycosuria, Hyperglycemia, glycosylated hemoglobin < 7, weight loss, recurrent infection(urinary tract, skin, and respiratory tract), Symptoms and sign of ketoacidosis in addition to above **(**Severe dehydration , a flushed face, fatigue, Smell of ketenes ,Acidotic breathing, blood sugar <350, Abdominal pain ,Vomiting ,Drowsiness and coma) [(16)]

Inclusion criteria

Patient who gathers these criteria enroll in this study.
1. first time and /or previously diagnosed type 1 diabetes **(**T1D**)**
2. Age between 1 and 16 years.
3. Both sexes

Exclusion criteria

1. any child take medication for type 1 diabetes other than insulin, Cholecalciferol (Vitamin D3) plus magnesium and zinc
2. Age below 1 and above 16 years.
3. Children who have renal disease
4. Children with malabsorption.
5. Children with type 2 diabetes **(**T2D**)**

Laboratory procedure

Investigations were done as baseline on admission and Follow-up 42 days which include CBP, LFT, RFT, random blood glucose, glycosylated hemoglobin, 25(OH) D, S. Mag.
Finest check to establish vitamin D status is the level of 25(OH) D [17] < 20 ng/mL (< 50 nmol/L): Vitamin D deficiency
Magnesium Normal range:
0.7–1 mmol/L (1.5–2 mEq/L; 1.7–2.4 mg/dL) [18]
Critical value: Less than 1 and more than 4.9 mg/dL
There is no test sensitive and specific to assess zinc in human [19]

STATISTICAL ANALYSIS done using SPSS version 21 Computer software to estimate rate, mean ± SD for both group by decrement of symptoms and sign of type 1 diabetes (T1D) and/or Symptoms and sign of ketoacidosis at 4 month and eight month from beginning of first admission for each patients. Compares 12 month overall reduction by mean±SD and P value in symptoms and sign of type 1 diabetes(T1D) and/or diabetic ketoacidosis in both group[20].

RESULTS

The fifty Child compares analysis symptoms and sign of type 1 diabetes (T1D) at 4 month the following: -

The Decrement in rate , mean,SD of symptoms and sign of type 1 diabetes (T1D) at 4 month of (Vitamin D3) plus magnesium and zinc group for Polydipsia11 9.5 (1.4), nocturnal polyurea 12 10.6(1.4), Glycosuria10 9.2 (1.1) , Hyperglycemia 10 8.2 (1.8), glycosylated hemoglobin < 7 12 9.6 (1.4), weight loss 11 9.8 (1.2), recurrent infection (UTI, SI, RTI) 10 8.4(1.6) , were significantly less than rate , mean,SD of symptoms and sign of type 1 diabetes (T1D) at 4 month of Placebo group for Polydipsia23 20.0(2.5),nocturnal polyurea 23 22.01 (1.95) , Glycosuria 21 19.52(1.48),Hyperglycemia24 20.74 (3.26), glycosylated hemoglobin < 7 22 19.66 (2.44), weight loss 24 20.64 (3.36) , recurrent infection (UTI, SI, RTI) 23 22.10 (1.90) as in table 1.

Table 1. compares analysis of Decrement in rate, mean, SD of Symptoms and sign of type 1 diabetes (T1D) at 4 month

Symptoms and sign of type 1 diabetes(T1D) at 4 month	Vitamin(D3) plus magnesium and zinc group25		Placebo group 25	
	N	Mean (S.D.)	N	Mean (S.D.)
Polydipsia	**11**	**9.5 (1.4)**	23	20.0 (2.5)
nocturnal polyurea	**12**	**10.6 (1.4)**	23	22.01 (1.95)
Glycosuria	**10**	**9.2 (1.1)**	21	19.52 (1.48)
Hyperglycemia	**10**	**8.2 (1.8)**	24	20.74 (3.26)
glycosylated hemoglobin < 7	**12**	**9.6 (1.4)**	22	19.66 (2.44)
weight loss	**11**	**9.8 (1.2)**	24	20.64 (3.36)
recurrent infection (UTI, SI, RTI)	**10**	**8.4 (1.6)**	23	22.10 (1.90)

The fifty Child compares analysis of Symptoms and sign of diabetic ketoacidosis at 4 month the following: -

The Decrement in rate , mean,SD of Symptoms and sign of diabetic ketoacidosis at 4 month of (Vitamin D3) plus magnesium and zinc group for Severe dehydration 13 11.9 (2.1) a flushed face 13 13.9 (2.1), Smell of ketones 13 9.5 (1.4), Acidotic breathing 11 10.9 (1.3) , blood sugar <350 10 8.93 (2.3), Abdominal pain 13 11.9 (2.1) , Vomiting 11 9.6 (1.4), Drowsiness 11 9.9 (1.1) , coma 12 10.8 (1.2) , were significantly less than rate , mean,SD of Symptoms and sign of diabetic ketoacidosis at 4 month of Placebo group for severe dehydration 24 21.7 (2.25), a flushed face 21 19.2 (1.8), Smell of ketones 23 20.5 (2.5) , Acidotic breathing 24 22.7 (2.25) , blood sugar <350 25 22.85 (2.15), Abdominal pain 22 20.0 (2.0), Vomiting 25 22.65 (2.35), Drowsiness 23 20.55 (2.45), coma 24 20.74 (3.26) as in table 2.

Table 2. compares analysis of Decrement in rate, mean, SD of Symptoms and sign of diabetic ketoacidosis at 4 month

Symptoms and sign of diabetic ketoacidosis at 4 month		Vitamin(D3) plus magnesium and zinc group25		Placebo group 25
Severe dehydration	**13**	**11.9 (2.1)**	**24**	**21.7 (2.25)**
a flushed face	**13**	**11.9 (2.1)**	**21**	**19.2 (1.8)**
Smell of ketones	**11**	**9.6 (1.4)**	**23**	**20.5 (2.5)**
Acidotic breathing	**11**	**10.9 (1.3)**	**24**	**21.7 (2.25)**
blood sugar <350	**10**	**8.93 (2.3)**	**25**	**22.85 (2.15)**
Abdominal pain	**13**	**11.9 (2.1)**	**22**	**20.0 (2.0)**
Vomiting	**11**	**9.6 (1.4)**	**25**	**22.65 (2.35)**
Drowsiness	**11**	**9.9 (1.1)**	**23**	**20.55 (2.45)**
coma	**12**	**10.8 (1.2)**	**24**	**20.74 (3.26)**

The fifty Child compares analysis symptoms and sign of type 1 diabetes (T1D) at 8 month the following: -

The Decrement in rate , mean,SD of symptoms and sign of type 1 diabetes (T1D) at 8 month of (Vitamin D3) plus magnesium and zinc group for Polydipsia 5 3.2 (1.8) , nocturnal polyurea 6 4.1 (1.9) , Glycosuria 5 4.0 (1.0) , Hyperglycemia 6 4.9 (1.3) , glycosylated hemoglobin < 7 5 3.2 (1.8) , weight loss 6 4.3 (1.7), recurrent infection (UTI, SI, RTI) 6 5.1 (0.9) ,were significantly less than rate , mean,SD of symptoms and sign of type 1 diabetes (T1D) at 8 month of Placebo group for Polydipsia 25 22.55 (2.45), nocturnal polyurea22 18.22 (3.82) ,Glycosuria 23 20.5 (2.5) ,Hyperglycemia24 21.75 (2.25), glycosylated hemoglobin < 7 25 22.65 (2.35) , weight loss23 21.0 (2.0), recurrent infection (UTI, SI, RTI) 24 21.7 (3.25) as in table 3.

Table 3. compares analysis of Decrement in rate, mean, SD of Symptoms and sign of type 1 diabetes (T1D) at 8 month

Symptoms and sign of type 1 diabetes(T1D) at 8 month	Vitamin(D3) plus magnesium and zinc group25			Placebo group25
	N	Mean (S.D.)	N	Mean (S.D.)
Polydipsia	**5**	**3.2 (1.8)**	**25**	**22.55 (2.45)**
nocturnal polyurea	**6**	**4.1 (1.9)**	**22**	**18.22 (3.82)**
Glycosuria	**5**	**4.0 (1.0)**	**23**	**20.5 (2.5)**
Hyperglycemia	**6**	**4.9 (1.3)**	**24**	**21.75 (2.25)**
glycosylated hemoglobin < 7	**5**	**3.2 (1.8)**	**25**	**22.65 (2.35)**
weight loss	**6**	**4.3 (1.7)**	**23**	**21.0 (2.0)**
recurrent infection (UTI, SI, RTI)	**6**	**5.1 (0.9)**	**24**	**21.7 (3.25)**

The fifty Child compares analysis of Symptoms and sign of diabetic ketoacidosis at 8 month the following: -

The Decrement in rate , mean,SD of Symptoms and sign of diabetic ketoacidosis at 8 month of (Vitamin D3) plus magnesium and zinc group for severe dehydration 4 3.8 (0.2) , a flushed face 5 3.2 (1.8), , Smell of ketones 6 5.1 (0.9), Acidotic breathing 5 4.3 (0.7), blood sugar <350 4 2.8 (1.2) , Abdominal pain 5 4.0 (1.0) , Vomiting 4 2.99 (1.1), Drowsiness 4 2.7 (1.3), coma 2 1.7(0.3), were significantly less than rate , mean,SD of Symptoms and sign of diabetic

ketoacidosis at 8 month of Placebo group for Severe dehydration 21 18.22 (2.82), a flushed face 25 22.11 (2.89), Smell of ketones 25 22.1 (2.9) , Acidotic breathing 23 20.5 (2.5) , blood sugar <350 25 22.85 (2.15) , Abdominal pain 24 20.75 (3.25) , Vomiting 25 21.7 (3.3), Drowsiness 23 20.5 (2.5), coma 24 20.74 (3.26) as in table 4.

Table 4. compares analysis of Decrement in rate, mean, SD of Symptoms and sign of diabetic ketoacidosis at 8 month

Symptoms and sign of diabetic ketoacidosis at 8 month		Vitamin(D3) plus magnesium and zinc group25		Placebo group25
Severe dehydration	4	3.8 (0.2)	21	18.22 (2.82)
a flushed face	5	3.2 (1.8)	25	22.11 (2.89)
Smell of ketones	6	5.1 (0.9)	25	22.1 (2.9)
Acidotic breathing	5	4.3 (0.7)	23	20.5 (2.5)
blood sugar <350	4	2.8 (1.2)	25	22.85 (2.15)
Abdominal pain	5	4.0 (1.0)	24	20.75 (3.25)
Vomiting	4	2.99 (1.1)	25	21.7 (3.3)
Drowsiness	4	2.7 (1.3)	23	20.5 (2.5)
coma	2	1.7(0.3)	24	20.74 (3.26)

The 12 month mean±SD overall reduction in symptoms and sign of type 1 diabetes (T1D) of (Vitamin D3) plus magnesium and zinc group was (92.84%) (23.21 ±1.56) which is more than in Placebo group (14.56%) (3.64±2.19) (P= 0.01) Additionally, the 12 month mean±SD overall reduction in symptoms and sign of diabetic ketoacidosis of (Vitamin D3) plus magnesium and zinc group was (90.88%) (22.72±1. 40) which is more than in Placebo group (9.76%) (11.44±2.81) (P= 0.01). As in Table (5) & Figure (1).

Table 5. Compares 12 month overall reduction by mean±SD and P value in symptoms and sign of type 1 diabetes(T1D) and/or diabetic ketoacidosis in both group

P value	Placebo group25 mean±SD	Vitamin(D3) plus magnesium and zinc group25 mean±SD	overall reduction at 12 month of type 1 diabetes (T1D)
0.01	3.64±2.19	23.21 ±1.56	overall reduction symptoms and sign of type 1 diabetes(T1D)
0.01	2.44±2.81	22.72±1. 40	overall reduction Symptoms and sign of diabetic ketoacidosis

*p < 0.05 is considered significant

Figure (1). Compares 12 month overall reduction by mean±SD in symptoms and sign of type 1 diabetes (T1D) and/or diabetic ketoacidosis in both group

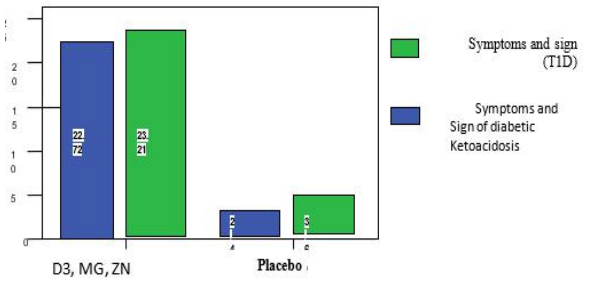

Figure 1. overall reduction

Discussion

This research is the first scientific established effectiveness of Cholecalciferol (Vitamin D3) plus magnesium and zinc in management of type 1 diabetes (T1D) in pediatric age group in Iraq. Obviously various trial of vitamin D3 alone, magnesium or zinc in different countries but no ultimate or definitive improvement in symptoms and sign of type 1 diabetes (T1D) and/or diabetic ketoacidosis is revealed in this study.

Reduction of symptoms and sign of type 1 diabetes(T1D) and/or Symptoms and sign of ketoacidosis at 4 month in Cholecalciferol (Vitamin D3) plus magnesium and zinc group were significantly higher than of Placebo group as shown table 1,2 which agree with result of Karamali M etel 2018 [21] . Jamilian M etel 2017 [22] , Takiishi T etel 2012[23], Dinesh G etel 2017[24] although our research give more accurate clinical and biomedical marker of tight glycemic control , this may be due to direct or indirect beneficial effects of (Vitamin D3) plus magnesium and zinc on insulin metabolism . Vitamin D3 effect may be due to the β-cells has vitamin D receptor (VDR) and genes controlling the vitamin D metabolism which concerned in the pathogenesis of type 1 diabetes (T1D) [23], link of regular vitamin D3 supplementation in early living and a decrease hazard for T1D [24] whereas vitamin D deficiency in early life is associated with a higher risk of T1DM later in life [25].

Magnesium is an essential cofactor of more than 300 enzymes including those important in glycolysis, transcellular ion transport(7), neuromuscular transmission, synthesis of carbohydrates, proteins, lipid and nucleic acids, and release of end response to certain hormones(8). effect on diabetics due to osmotic diuresis cause high renal excretion of magnesium, and insulin insensitivity that affects intracellular magnesium transport(26) and causes increased loss of extracellular magnesium so in our study magnesium supplement induce perfection of insulin sensitivity and decrement of symptoms and sign of type 1 diabetes(T1D) (27) decline of symptoms and sign of type 1 diabetes(T1D) and/or ketoacidosis at 8 month in Cholecalciferol (Vitamin D3) plus magnesium and zinc group were significantly higher than of Placebo group as shown table 3,4 that consent with result of Jamilian M 2017 (22), Jayawardena R 2012 (14) . This may elucidate the importance of zinc dyshomeostasis, resulting from inadequate dietary intake or genetic causes, in the progress of T1D. Zinc has insulin like effects on cells by support of lipogenesis and promotion of glucose transport. This suggests that zinc may stimulate tissues to : improve insulin signaling, use glucose, maintain normal lipid metabolism and maintain normal cellular functions And Our research disagree with Ching-Chiang Lin 2015 (28).

In the present study notice that improvement in clinical picture of T1D and/or DKA where more obvious (mean±SD) in 8 months than in 4 months as shown on table 1,2,3,4 this may be due to full normalization of vitamin D_3 magnesium, zinc on T1D

In the present research overall reduction at 12 month symptoms and sign of type 1 diabetes (T1D) and/or ketoacidosis of (vitamin D_3 magnesium, zinc) group were significantly higher than of placebo group as shown table 5,

figure (1) which may be due to all above mentioned reason in discussion and normalization and/or synergistic effect of vitamin D_3 magnesium, zinc on tight glycemic control [29].
Neither side effect nor complication encounter in study period for (vitamin D_3 magnesium, zinc) group.
The limitation of study is small size and not estimating zinc level as explanation in Laboratory procedure. Also no exact similar study of (vitamin D_3 magnesium, zinc) in management of type 1 diabetes (T1D) in pediatric age group in deferent scientific web site or even textbook and for that is had to compare with adult research[30]

Conclusion

Cholecalciferol (Vitamin D3) plus magnesium and zinc can be safe and effective used for tight glycemic control and decrement in symptoms and sign of type 1 diabetes (T1D) and/or diabetic ketoacidosis in pediatric age group

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