Introduction

Lifelong steroid replacement has to be maintained in subjects with congenital adrenal hyperplasia (CAH), to decrease the overall excessive production of androgens by the adrenal gland, and to provide the everyday cortisol needs [1]. Optimizing steroid dosing is crucial in children to enhance growth outcome, bone health and hence improve quality of life. Patients with classic CAH have an increased frequency of growth suppression, obesity especially visceral adiposity, elevated insulin levels, Insulin resistance (IR), hyperandrogenism, and peripheral precocious puberty that might trigger activation of the hypothalamic-pituitary axis prematurely, compared to normal individuals [2]. Abnormal adenomедullary function and periods of intermittent hypercortisolism, due to the use of supraphysiological doses of corticosteroid during treatment, may contribute to the development of these aberrations and increase the risk of developing metabolic derangements especially metabolic syndrome (MetS) and atherosclerosis in those patients [3].

Vitamin D has a crucial impact on keeping calcium/phosphorus homeostasis. However, other possible extraskeletal functions of 25-hydroxy Vitamin D (25(OH)D3) are emerging [3]. Numerous researchers have disclosed the immunomodulatory effects of 25(OH)D3 [4] and that 25(OH)D3 deficiency may be accompanied by a state of sub-inflammation, IR, and MetS. These conditions are all considered insulin-resistant states, in which different chemical substances such as hormones and cytokines are involved. However, all these pathologic conditions are characterized by of chronic sub-inflammatory state [5]. Sub-inflammation has a crucial role in the development of IR and obesity/MetS, and it has been hypothesized that 25(OH)D3 deficiency might contribute to it [6].

Both insulin action and secretion have been thought to be influenced by optimal 25(OH)D3 levels [7]. It might not have a direct effect on IR; however, it could be through its favorable effects on glucocorticoids and evolution of metabolic derangements.
regulating the calcium homeostasis, and adjusting cytokine expression and activity. All these mechanisms may account for the beneficial effect of 25(OH)D3 on insulin action in peripheral tissues [6]. Data from studies including human participants also indicate that low levels of 25(OH)D3 are associated with impaired function of β-cells of Islets of Langerhans, IR, and poor glucose tolerance [8].

Numerous studies also indicated a reversed association between serum levels of 25(OH)D3 and fasting plasma glucose, IR, and lipid panel except for HDL-cholesterol [5] which demonstrate the beneficial effect of administering 25(OH)D3. However, evidence is still contradictory regarding its influence [9]. A number of interventional trials proposed that we are still lacking proof concerning the favorable effect of 25(OH)D3 on metabolic aberrations especially IR [10]. Others indicated the lack of favorable impact of Vitamin D intake on metabolic profile [11].

Many studies have assessed the levels of 25(OH)D3 in patients with CAH and have detected low levels especially in pubertal females compared to healthy controls [12]. In addition, a Turkish study was conducted to detect the prevalence and association between 25(OH)D3 deficiency and bone density in individuals with CAH. This study detected the presence of significantly lower 25(OH)D3 in females than in males especially during puberty [12]. However, the impact of Vitamin D replacement therapy on metabolic derangements in CAH patients has not been explored. Therefore, this pilot aimed at identifying the serum 25(OH)D3 status in female patients with CAH who are following up at Diabetes Endocrine and Metabolism Pediatric Unit (DEMPU) clinic at Abou ElRish Children’s Hospital, Cairo University and to detect the presence of metabolic abnormalities in those patients. We also examined the association between both aspects and the impact of Vitamin D supplementation on metabolic abnormalities as a mean to enhance the quality of life in those girls.

Patients and Methods

Patients

Our study was conducted between May 2016 and January 2017 (9 months duration), 16 female patients with classic CAH who were managed at DEMPU, Abou ElRish Children’s Hospital, Cairo University were recruited, and verbal consent was obtained. Patients with clinical and laboratory diagnosis of classic CAH (salt-wasting) and age ≥ 8 and < 18 years were recruited. The study included only subjects with Vitamin D insufficiency or deficiency. All participants had a stable condition and were not receiving any medications other than steroids that might affect the secretion of androgen or bone metabolism. Patients who had sufficient Vitamin D or on Vitamin D therapy were excluded from the study. The present study was approved by the bioethical research committee, Faculty of medicine, Kasr Alainy University Hospitals, Cairo, Egypt (approval number: I-100315).

After explanation of the methodology and obtaining verbal informed consent or assent from the patient and/or the patient’s legal guardians, all included subjects were evaluated as follows:

- Thorough clinical examination to detect any associated conditions or complications, including anthropometric assessment and growth velocity during the study period (GV). Weight (kg) was measured using a Seca Scale balance and approximated to the nearest 0.1 kg. Standing height (cm) was measured using Harpenden stadiometer and approximated to the nearest 0.1 cm. Weight and height readings were then plotted against the Egyptian growth curves [13]. Standard deviation scores (SDS) for the above measurements were assessed by the growth vision computer software provided by Novo Nordisk.

- Pubertal staging was assessed using Tanner maturity scale [14].

- Patients were examined for signs of hyperandrogenism including hirsutism, acne vulgaris, weight gain, and menstrual irregularities [15]. Hirsutism was scored using Modified Ferriman–Gallwey score of ≥ 8 is considered hirsutism [16].

- The dose of glucocorticoids was expressed as mg/m²/day and the mean dose was calculated over the 1 year before recruitment. Overtreatment or the use of supraphysiological doses was defined as the use of hydrocortisone of more than 15 mg/m²/day.

Laboratory investigations

Venous blood samples were obtained from all patients following an overnight fast of 8–12 h before 25(OH)D3 supplementation to measure serum levels of 25(OH)D3, fasting serum insulin, fasting serum glucose, and 17 hydroxyprogesterone (17-OHP). Serum 25(OH)D3 levels were assessed using enzyme-linked immunosorbent assay (ELISA) based on the principle of competitive binding. Vitamin D status of patients was determined according to the 25(OH)D3 levels. Levels of serum 25(OH)D3 levels above 30 ng/mL were considered normal. Levels of 10–29 ng/mL were insufficient and levels < 10 ng/mL were considered deficient [17]. Fasting serum insulin was assessed using Tosoh Bioscience AIA-360 System, AIA-360 Immunoassay System Diagnostic test. Reference range < 17 uU/ml according to the kit was used by Tosoh Bioscience, Inc. Fasting blood glucose (mg/dl) was assayed by GOD-POD method which is an in vitro test for the quantitative assay of glucose concentration.
in serum by photometric system [18]. 17-OHP (ng/mL) was measured by ELISA using competitive method [19]. Serum 17-OHP levels of 1–10 ng/mL were acceptable [20]. Therefore, in this study, we considered patients with serum 17-OHP levels ≤ 10 were controlled and > 10 were uncontrolled cases.

The following IR sensitivity and resistance indices were calculated:

- **HOMA-IR** was calculated according to the following equation [21]:
  \[
  \text{HOMA-IR} = \frac{\text{Insulin} \times \text{Glucose}}{22.5}
  \]
  where Insulin (mIU/L) and Glucose (mmol/L) are fasting levels.

- **HOMA-S** (Homeostasis model assessment of IR sensitivity) was equal to 1/HOMA-IR.

- **HOMA-B** (Homeostasis model assessment of beta cell function) was determined as follows [23]:
  \[
  \text{HOMA-B} = \frac{\text{Insulin} \times \text{Glucose}}{22.5}
  \]

- **IR sensitivity** was measured using the quantitative Insulin sensitivity check index (QUICKI) [24]:
  \[
  \text{QUICKI} = \frac{1}{\log \text{Insulin} - \log \text{Glucose}}
  \]

Then, cholecalciferol was given to all patients in the form of oral daily doses (Decal B12 syrup) for 6 months (4000 IU for patients aged from 8 to 12 years, 6000 IU for patients aged more than 12 years old) [26].

Follow-up was done after 6 months of cholecalciferol therapy, physical examination was repeated including anthropometric measurements, clinical assessment was done to detect any change in Tanner staging, signs of hyperandrogenism, and hirsutism scoring. Laboratory investigations were done including 17-OHP, 25(OH)D3, fasting Insulin, fasting glucose with calculation of the HOMA-IR, HOMA-B, HOMA-S, and QUICKI.

### Statistical methods

Statistical analysis was done using SPSS 22 (IBM Corp, Armonk, NY, USA). Categorical data were compared using Chi-square test. Independent sample t-tests or Mann–Whitney U tests were used for measured data when appropriate. Within group, comparison of numerical variables was done using Wilcoxon signed rank test for paired (matched) samples. Exact test was used instead when the expected frequency is < 5. McNemar test was used to compare between pre- and post-treatment, correlation between various variables was done using Spearman rank correlation equation. P < 0.05 was considered statistically significant.

### Results

Our study included 16 adolescent females with classic CAH. Anthropometric, clinical, and laboratory data of the studied cases prior to and after Vitamin D therapy are shown in (Tables 1 and 2) and (Figure 1). Mean 25(OH)D3 levels before and after treatment were 16.35 ± 5.24 ng/mL and 30.8 ± 10.6 ng/mL, respectively (p = 0.0001; Table 2). The whole group (16 participants) had 25(OH)D3 levels below 30 ng/mL; 13 patients (81.3%) had insufficient 25(OH)D3 levels: 10–29 ng/mL; and 3 patients (18.7%) had deficient 25(OH)D3 levels (levels < 10 ng/mL) before treatment, and after the treatment, none of the participants had 25(OH)D3 deficiency. 8 patients (50%) had 25(OH)D3 insufficiency, and 8 patients (50%) had normal 25(OH)D3 levels (Table 1). Regarding the anthropometric data, there were statistically significant differences between BMI, BMI SDS, weight, weight SDS, height, and height SDS before and after Vitamin D (p = 0.009, 0.024, 0.005, 0.048, 0.019, and 0.019 respectively). There was no significant difference regarding other laboratory data and steroid doses before and after Vitamin D (Table 2). Vitamin D levels correlated negatively with each of the weight SDS before and height SDS after Vitamin D therapy reaching statistical significance (p = 0.02 and 0.027, respectively) (Table 3). Low height SDS despite of improvement of 25(OH)D3 level might be due to the negative impact of steroid doses.
prolonged administration of supraphysiological doses of steroids on height especially during puberty which is a long-term effect. In addition, statistically significant positive correlation was found between HOMA-IR and IR level and HOMA-B before and after Vitamin D supplementation ($p = 0.0001$ for each) (Table 4). When correlating HOMA-IR with the other parameters, a statistically significant negative correlation was detected between HOMA-IR and each of HOMA-S and QUICKI both before and following Vitamin D therapy ($p = 0.0001$ for each) (Table 4). No statistically significant correlation between the steroid dose and all laboratory and anthropometric data was found before Vitamin D therapy.

**Discussion**

Researchers have been studying the effect of 25(OH)D3 status on Insulin resistance (IR) for years [27]. CAH patients, compared with normal individuals with the same BMI, are more prone for the development of IR and greater insulin levels. This fact may be related to the long-term disturbance of adrenomedullary function, higher androgen concentrations, and glucocorticoid replacement therapy [28].

To the best of our knowledge, the impact of Vitamin D administration on IR in pubertal females with CAH was not investigated before. However, its effect on IR in populations other than CAH, such as polycystic ovarian syndrome that has higher than normal levels of androgens and IR, has been well investigated. Additionally, in populations with Type 2 diabetes mellitus, it has been well explored.

In the present study, a remarkable rise in 25(OH)D3 levels was observed after administration ($p = 0.0001$); however, this was not associated with notable changes in insulin, glucose, HOMA-S, HOMA-IR, HOMA-B, and QUICKI. These findings were similar to that observed in a randomized controlled trial (RCT) conducted in 2015 including adult T2DM patients indicating that despite the significant rise in serum levels of 25(OH)D3 ($p \leq 0.01$) detected, there were no statistically significant differences observed in other aspects including HOMA-IR, HOMA-B, QUICKI, fasting glucose, and fasting insulin [29]. Similarly, another RCT conducted in patients with T2DM and 25(OH)D3

**Table 2: Comparison between anthropometric and laboratory data before and after Vitamin D therapy**

| n=16 cases | Before Vitamin D therapy | After Vitamin D therapy | P value |
|-----------|--------------------------|-------------------------|---------|
| Vitamin D (ng/ml) | 16.35 ± 5.24 | 30.8 ± 10.6 | 0.0001 |
| Insulin (uU/ml) | 12.83 ± 9.39 | 14.8 ± 11.49 | 0.301 |
| Glucose (mg/dL) | 94.2 ± 11.5 | 89.6 ± 9.3 | 0.093 |
| HOMA-IR | 3.05 ± 2.5 | 3.24 ± 2.74 | 0.518 |
| HOMA-S | 0.52 ± 0.34 | 0.7 ± 0.8 | 0.569 |
| HOMA-B | 2.86 ± 1.86 | 3.39 ± 2.5 | 0.326 |
| QUICKI | 0.33 ± 0.03 | 0.34 ± 0.04 | 0.731 |
| BMI | 23.8 ± 5.6 | 25.5 ± 5.5 | 0.009 |
| BMI SDS | 1.40 ± 1.18 | 1.74 ± 1.05 | 0.024 |
| Weight (kg) | 51.13 ± 16.5 | 55.8 ± 16.4 | 0.005 |
| Weight SDS | 0.96 ± 1.65 | 1.3 ± 1.68 | 0.048 |
| Height (cm) | 144.9 ± 12.5 | 146.4 ± 11.5 | 0.019 |
| Height SDS | −0.98 ± 1.45 | −1.18 ± 1.13 | 0.019 |
| Growth velocity SDS | −0.46 ± 1.18 | −1.24 ± 1.82 | 0.059 |
| Steroid dose (mg/m²) | 18.05 ± 2.82 | 17.99 ± 4.67 | 0.691 |

Data are expressed as mean ± SD. BMI SDS: Body mass index standard deviation score. 17 OH Progesterone: 17 hydroxyprogesterone. HOMA-IR: Homeostatic model assessment-insulin resistance and is equal to fasting insulin level (uU/ml) × the fasting glucose level (mmol/l)/22.5. HOMA-B: homeostasis model assessment of beta cell function and is equal to fasting insulin (mU/l) × 20/fasting glucose (mmol/l−3.5). HOMA-S: homeostasis model assessment of insulin sensitivity and is equal to 1/HOMA-IR. QUICKI: quantitative insulin sensitivity check index and is equal to 1/log I₀−log G₀, where I₀ is fasting insulin (mU/l) and G₀ is fasting glucose (mg/dl). Significant if $P < 0.05$. 

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Figure 1: Comparison between anthropometric and laboratory data before and after Vitamin D therapy
Table 3: Correlations between Vitamin D and other laboratory and anthropometric data before and after supplementation

| Vitamin D (ng/ml) | Before | Correlation | p value | After  | Correlation | p value |
|------------------|--------|-------------|---------|--------|-------------|---------|
| Insulin (U/L)    | -0.14  | 0.051       | 0.18    | 0.018  | 0.948       | 0.001   |
| Glucose (mg/dl)  | 0.99   | 0.001       | 0.989   | 0.001  | 0.989       | 0.001   |
| HOMA-IR          | 0.162  | 0.546       | 0.204   | 0.45   | 0.001       | 0.001   |
| HOMA-S           | -1     | 0.0001      | 1       | 0.001  | -1          | 0.001   |
| HOMA-B           | 0.947  | 0.001       | 0.966   | 0.001  | 0.966       | 0.001   |
| QUICKI           | -0.994 | 0.0001      | 0.995   | 0.0001 | 0.995       | 0.0001 |
| 17OH Progesterone (ng/ml) | 0.209 | 0.437 | 0.342 | 0.195 |
| Steroid dose (mg^2) | -0.05 | 0.054 | 0.819 | 0.471 |
| BMI              | 0.186  | 0.49        | 0.209   | 0.438  | 0.001       | 0.001   |
| BMI SDS          | 0.275  | 0.303       | 0.265   | 0.321  | 0.001       | 0.001   |
| Weight (kg)      | 0.143  | 0.598       | 0.047   | 0.862  | 0.001       | 0.001   |
| Weight SDS       | 0.364  | 0.165       | 0.322   | 0.224  | 0.001       | 0.001   |
| Height (cm)      | 0.196  | 0.466       | -0.088  | 0.745  | 0.001       | 0.001   |
| Height SDS       | 0.366  | 0.163       | 0.283   | 0.289  | 0.001       | 0.001   |

Table 4: Correlations between HOMA-IR and other laboratory and anthropometric data before and after Vitamin D therapy

| Vitamin D (ng/ml) | Before | Correlation | p value | After  | Correlation | p value |
|------------------|--------|-------------|---------|--------|-------------|---------|
| Insulin (U/L)    | -0.14  | 0.051       | 0.18    | 0.018  | 0.948       | 0.001   |
| Glucose (mg/dl)  | 0.99   | 0.001       | 0.989   | 0.001  | 0.989       | 0.001   |
| HOMA-IR          | 0.162  | 0.546       | 0.204   | 0.45   | 0.001       | 0.001   |
| HOMA-S           | -1     | 0.0001      | 1       | 0.001  | -1          | 0.001   |
| HOMA-B           | 0.947  | 0.001       | 0.966   | 0.001  | 0.966       | 0.001   |
| QUICKI           | -0.994 | 0.0001      | 0.995   | 0.0001 | 0.995       | 0.0001 |
| 17OH Progesterone (ng/ml) | 0.209 | 0.437 | 0.342 | 0.195 |
| Steroid dose (mg^2) | -0.05 | 0.054 | 0.819 | 0.471 |
| BMI              | 0.186  | 0.49        | 0.209   | 0.438  | 0.001       | 0.001   |
| BMI SDS          | 0.275  | 0.303       | 0.265   | 0.321  | 0.001       | 0.001   |
| Weight (kg)      | 0.143  | 0.598       | 0.047   | 0.862  | 0.001       | 0.001   |
| Weight SDS       | 0.364  | 0.165       | 0.322   | 0.224  | 0.001       | 0.001   |
| Height (cm)      | 0.196  | 0.466       | -0.088  | 0.745  | 0.001       | 0.001   |
| Height SDS       | 0.366  | 0.163       | 0.283   | 0.289  | 0.001       | 0.001   |

On the other hand, several studies reported that Vitamin D administration decreased insulin as in the one carried out to detect the impact of Vitamin D replacement on indices of IR in females aged 20–40 years diagnosed with PCOS and deficient in 25(OH)D3 where it was reported that a single injection (300,000 IU) leads to a significant elevation in 25(OH)D3 (p < 0.001) associated with a remarkable decline in fasting plasma glucose levels, fasting insulin levels, and HOMA-IR (p = 0.003, 0.019, and 0.004, respectively) [33]. Similarly, a significant decline of serum fasting plasma glucose levels and HOMA-IR (p < 0.01 for both) was associated with a significant elevation in serum 25(OH)D3 following supplementation of healthy Japanese participants with Vitamin D in a double-blind RCT conducted in 2016. Moreover, fasting serum insulin level was reduced but did not reach statistical significance [34]. Another study carried out including 100 participants with T2DM, showed that administration of Vitamin D supplements reduced fasting blood glucose, insulin, and HOMA-IR significantly (p = 0.05, 0.028, and 0.008, respectively) [35].

Another RCT conducted including 28 women with PCOS. They were randomly allocated in one of two groups; one group was receiving oral Vitamin D3 and the other was consuming placebo for 3 months. A significant rise in 25(OH)D3 level was detected in the Vitamin D group (p ≤ 0.001) but no statistically significant changes have been observed in the fasting plasma glucose and IR levels, HOMA-S, HOMA-IR, and QUICKI in the Vitamin D group after supplementation. However, a significant rise in HOMA-B in this group after treatment was noted (p = 0.01) [31]. Another study reported that supplementation of PCOS females who had 25(OH)D3 deficiency significantly increased the serum levels of 25(OH)D3 and HOMA-B (p = 0.001 and 0.014, respectively), whereas fasting plasma glucose was significantly decreased (p = 0.001) [32]. In the present study, an increase in HOMA-B following Vitamin D supplementation was detected, but it did not reach statistical significance (p = 0.326).
find studies that have investigated the effect of Vitamin D supplementation on the studied correlations.

**Study limitations**

The present study had some limitations including the small sample size with short duration of supplementation that may have contributed to the fact that only 50% of the participants reached sufficient 25(OH)D3 levels after supplementation, additionally, the serum calcium level before and after the study was not assessed and Vitamin D polymorphism could not be evaluated. During previous studies, various researchers contributed the lack of sufficient evidence of the impact of Vitamin D supplementation to the insufficient dose and duration of Vitamin D administration [39,40] in addition to the small sample size [41].

**Conclusion**

Vitamin D replacement therapy did not have favorable effects on IR and other insulin sensitivity indices in females with CAH. Future research using RCT is required to examine the impact of 25(OH)D3 on IR, which might influence the production of adrenal androgen, resulting in reduction of the therapeutic effect of glucocorticoids that might play a part in to the evolution of MetS.

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