Autoimmunity, Insulin-Resistance, Non-Classic Adrenal Hyperplasia, and Vitamin D

Alan Sacerdote*

Chief, Endocrine Division, NYC Health+Hospitals/Woodhull Clinical Professor of Medicine, SUNY Downstate Medical Center& NYU School of Medicine Professor of Medicine, St. George's University, Brooklyn, New York, USA

AUTOIMMUNITY IS ASSOCIATED WITH NON-CLASSIC ADRENAL HYPERPLASIA

Patients with these autoimmune disorders have been reported to generally have non-classic adrenal hyperplasia (NCAH):

- Type 1 diabetes mellitus [1]
- Graves' disease [2]
- Hashimoto's thyroiditis [3]
- Vitiligo [4]
- Psoriasis [5]
- Rheumatoid arthritis [6]

Non-classic adrenal hyperplasia (NCAH) is universally encountered in type 2 Diabetes mellitus (T2DM) with the exception of people who have no family history of T2DM and developed T2DM after hepatitis C Virus infection [7].

Recently, it has been reported that about 2/3 of patients with T2DM have evidence of autoimmunity, when highly sensitive tests for cellular autoimmunity are employed [8]. A recent report showed that in T2DM patients metabolic balance, low density lipoprotein (LDL) cholesterol and cardio C-reactive protein (CRP) levels as well as waist/hip ratio (WHR) are contributing to the exacerbation of inflammation by increasing the production of pro-inflammatory cytokines, including interleukin (IL-34) [9].

One possible reason for this apparent connection between NCAH and autoimmune disorders may be that serum cortisol levels, in general, are lower in CAH patients, than in the general population and cortisol and its analogues remain a pillar of treatment in the anti-autoimmune arsenal. Thus, autoimmunity may, to an extent be the result of chronically low serum/tissue cortisol.

Non-Classic Adrenal Hyperplasia is Associated with Insulin Resistance

While the association of polycystic ovarian syndrome (PCOS) with insulin resistance (IR) is generally accepted, the equally important association of NCAH and classic congenital adrenal hyperplasia (CAH) with IR is less widely known, even among endocrinologists [10-13].

Insulin Resistance is Associated with Autoimmunity

Insulin resistance, in turn, has been associated with increased risk of developing autoimmune disorders [14-18].

The Gut Microbiome is Similar in Insulin Resistance and Autoimmunity

Insulin resistance and a number of autoimmune disorders are associated with similar changes in the intestinal microbiome, viz decreased bacterial numbers and species diversity [19].

A Similar Th-1 Dominant Cytokine Profile is Encountered in both Patients with Autoimmune Disorders and those with Insulin Resistance

Inflammatory cytokines are involved in pathogenesis of both autoimmune disorders and insulin resistance [20-33].

Serum 25-OH-Vitamin D Levels are Lower in Patients with Disorders Linked to Insulin Resistance

Serum Vitamin D levels have been reported to be lower in patients with disorders usually associated with

*Address correspondence to this author at the Chief, Endocrine Division, NYC Health+Hospitals/Woodhull Clinical Professor of Medicine, SUNY Downstate Medical Center& NYU School of Medicine Professor of Medicine, St. George's University, Brooklyn, New York, USA; Tel: +13476458255;
E-mail: Alan.Sacerdote@woodhullhc.nychhc.org

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insulin resistance like, T2DM, Polycystic Ovarian Syndrome (PCOS), NCAH, CAH, Alzheimer's Disease, Eclampsia and Preeclampsia [34-48].

Vitamin D Receptor Polymorphisms are Associated with the Pathogenesis and/or Severity of Several Autoimmune Disorders

In some autoimmune disorders polymorphisms of the Vitamin D Receptor (VDR) have been associated with susceptibility to the disorder or a more severe clinical course [49].

Vitamin D Supplementation may Ameliorate and/or Prevent Certain Autoimmune Disorders

Supplementation with 1,25 OH Vit. D, the active form of Vitamin D, has been shown to lower the concentration of tumor necrosis factor alpha (TNF-α) in a rodent model of T2DM [50]. Evidence of Vitamin D repletion in prevention and treatment of autoimmune disorders other than vitiligo and psoriasis is conflicting [51-57]. One study has shown a dose-effect of Vitamin D supplementation in infants of >7 months old in the prevention of type 1 Diabetes Mellitus (T1DM) [58].

Another randomized control study showed a benefit from Vitamin D supplementation in Systemic Lupus Erythematosus (SLE) patients on inflammatory and hemostatic markers and disease activity [59].

Overall there is good epidemiologic evidence that low serum 25-OH-Vitamin D levels and/or VDR polymorphisms are associated with increased risk for development of and increased severity of most, if not all, autoimmune disorders. Many more randomized, control, prospective studies are needed to assess the effects of Vitamin D repletion/supplementation on the prevention and treatment of autoimmune disorders.

Vitamin D Repletion has been Associated with Amelioration of PCOS, NCAH, CAH

Rashidi *et al.* [60] have reported an independent benefit of vitamin D supplementation in women with PCOS equivalent to that observed with metformin as well as an additive benefit when combined with metformin. Sacerdote *et al.* [61-64] have reported amelioration of classic 11-hydroxylase deficiency (Figures **1**,**2**), non-classic 11-hydroxylase deficiency (Figure **3**), and non-classic 21-hydroxylase deficiency with Vitamin D repletion.

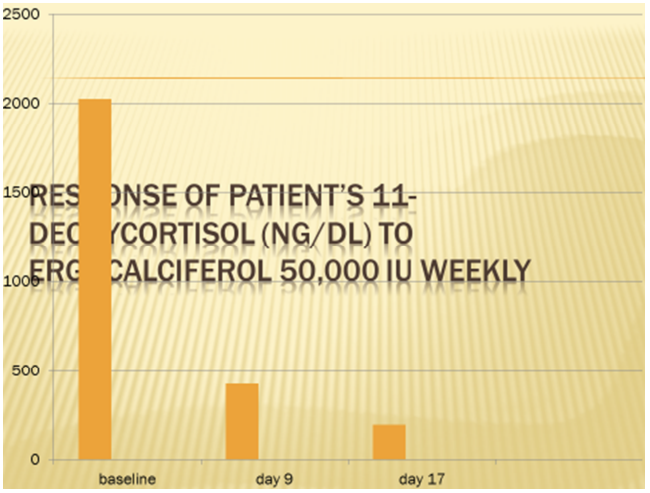


Figure 1: Response of serum 11-deoxycortisol (ng/dl) to vitamin D repletion in a patient with classic 11-hydroxylase deficiency and Vitamin D deficiency.

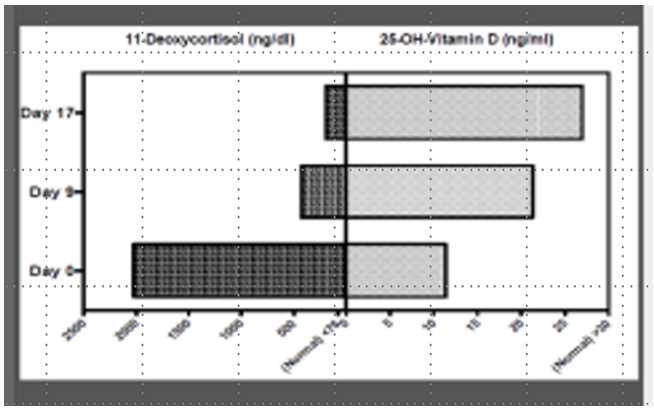


Figure 2: Serum 11-deoxycortisol as a function of serum 25-OH-Vitamin D in a patient with classic 11-hydroxylase deficiency and Vitamin D deficiency.

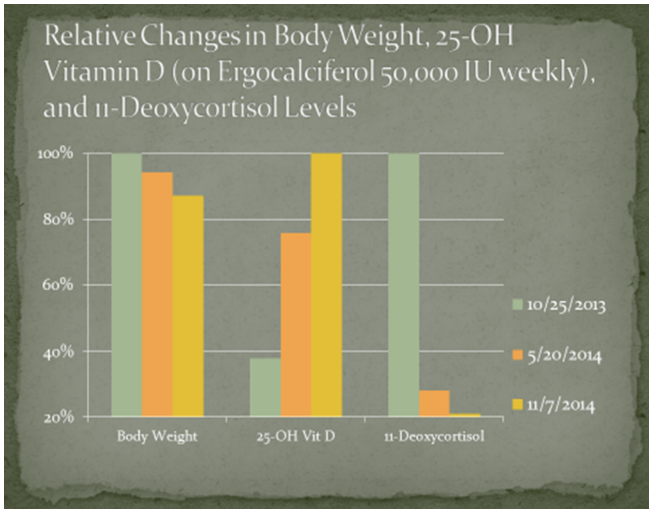


Figure 3: Relative % changes in body weight, serum 25-OH-Vitamin D, and serum 11-deoxycortisol in a patient with non-classic 11-hydroxylase deficiency and Vitamin D deficiency from baseline with Vitamin D repletion.

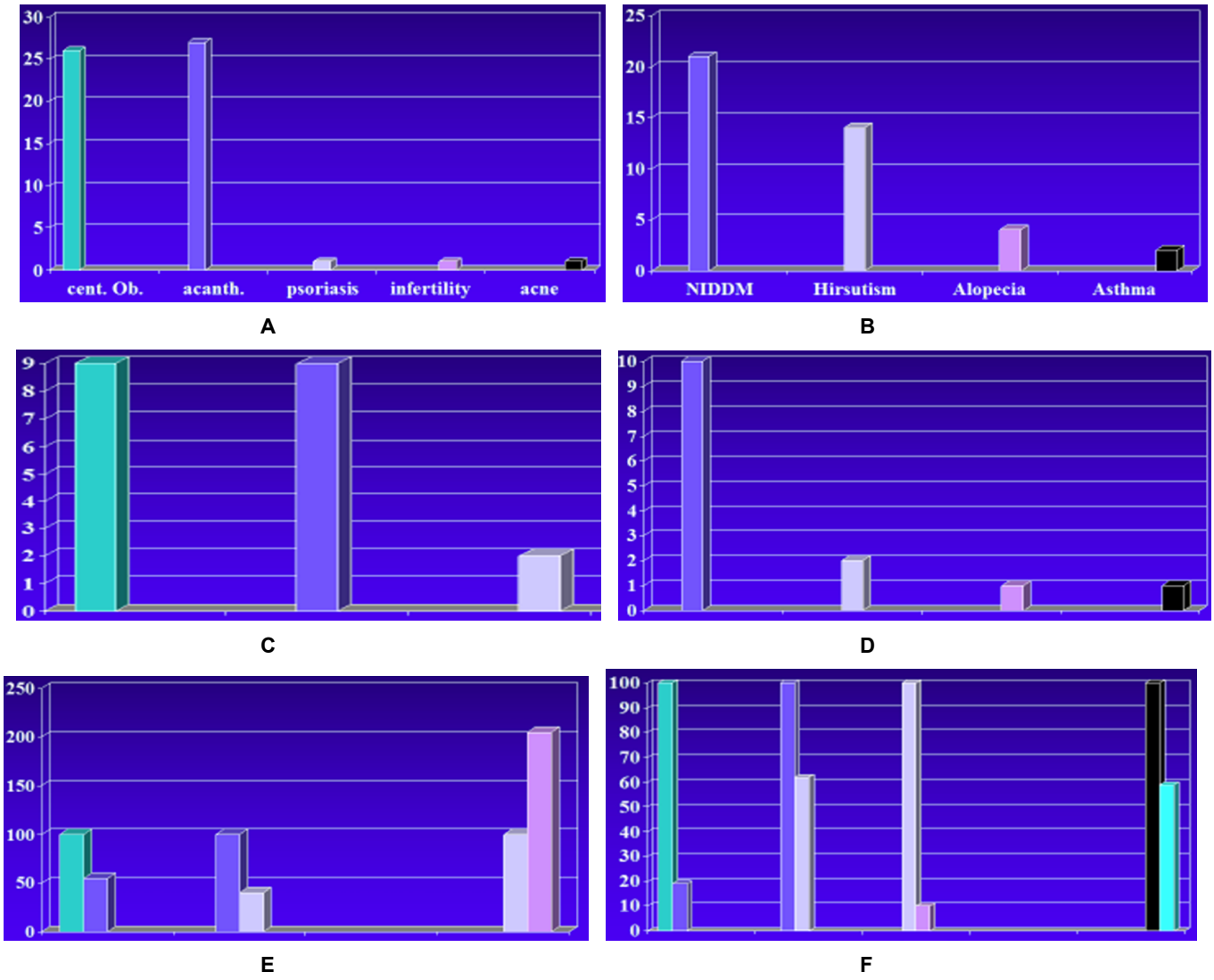


Figure 4: A. Clinical features of patients with abnormal glucose tolerance with numbers of affected patients. Cent. Ob.=central obesity, acanth.=acanthosis nigricans.

B. Clinical features of patients with abnormal glucose tolerance with numbers of affected patients-continued. NIDDM=non-insulin-dependent diabetes mellitus, an older name for T2DM.

C. Numbers of patients with abnormal glucose tolerance and elevated serum steroid metabolites. Left to right-17-OH-progesterone, 17-OH-pregnenolone, 11-deoxycortisol.

D. Numbers of patients with abnormal glucose tolerance with low sex hormone binding globulin or elevated serum steroid metabolites. Left to right- decreased sex hormone binding globulin, high serum estrone, high serum DHEA, high deoxycorticosterone.

E. Percent changes in elevated steroid metabolites or low sex hormone binding globulin (SHBG) with treatment with the insulin sensitizers, metformin+troglitazone, in patients with abnormal glucose tolerance. Left to right 17-OH-progesterone, 17-OH-pregnenolone, SHBG.

F. percent changes in elevated serum steroid metabolites in patients with abnormal glucose tolerance when treated with the insulin sensitizers metformin+troglitazone. Left to right estrone, DHEA, 11-deoxycortisol, deoxycorticosterone.

Other Insulin Sensitizing Interventions Ameliorate NCAH

In a study of 33 patients with NCAH and Type 2 diabetes mellitus (T2DM), or pre-diabetes, aged 29 – 75 years old, 6 males, 27 females treated with either metformin alone or metformin plus the peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist troglitazone, the use of these insulin sensitizers resulted in biochemical and clinical amelioration of NCAH [65] (Figures **4A-4F**). Interestingly, NCAH responded to insulin sensitizers metformin + troglitazone regardless of which type of NCAH the patient had.

Weight loss may favorably affect the expression of NCAH much as it may reduce the incidence and severity of several autoimmune disorders. We reported our experience with 2 patients with aldosterone synthase deficiency (ASD), a form of NCAH we first described in 1999 [66]. The patients were 2 women, 36 and 41 years old respectively, both with central obesity and hirsutism. Their mean baseline weight was:88 kg and mean baseline BMI was 32 kg/m^2. Mean baseline serum deoxycorticosterone (DOC) was 15 ng/dl (1.5 – 13ng/dl). Mean baseline luteinizing hormone/follicle stimulating hormone (LH/FSH) Ratio: 2.2 (<1). The association of weight loss from lifestyle changes (nutritional and exercise) with (body mass index) BMI, serum DOC and LH/FSH ratio is shown in Figure **5** below [67].

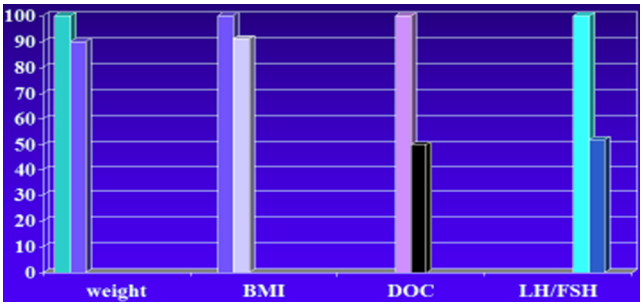


Figure 5: association of lifestyle induced weight loss with changes in BMI, DOC, and LH/FSH in 2 women with non-classic aldosterone synthase deficiency.

We have also reported that Roux-en-Y gastric bypass surgery achieved and maintained normalization of serum 11-deoxycortisol in a patient who had non-classic 11-hydroxylase deficiency in association with Type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia [68] (Figure **6**).

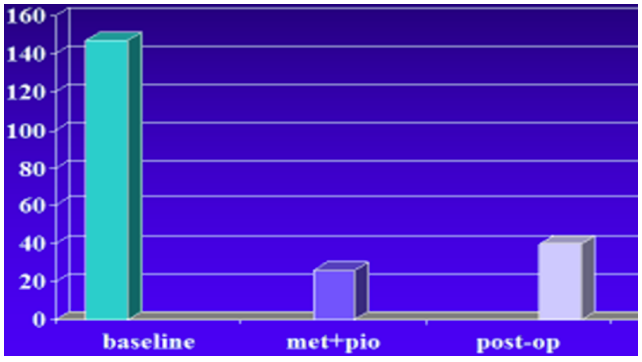


Figure 6: Left to right baseline serum 11-deoxycortisol (ng/dl) at baseline, serum 11-deoxycortisol on the insulin sensitizers metformin+pioglitazone, 5 weeks-post-bariatric surgery off medications serum 11-deoxycortisol (ng/dl).

The Ayurvedic preparation, Ashwagandha root, *Withania somnifera,* which has been reported to be an insulin sensitizer [69], has been reported to induce biochemical and clinical remission of non-classic aldosterone synthase deficiency (Figure **7a**) and non-classic 3-β-ol-dehydrogenase deficiency (Figure **7b**) in a woman complaining of increased scalp hair loss [70].

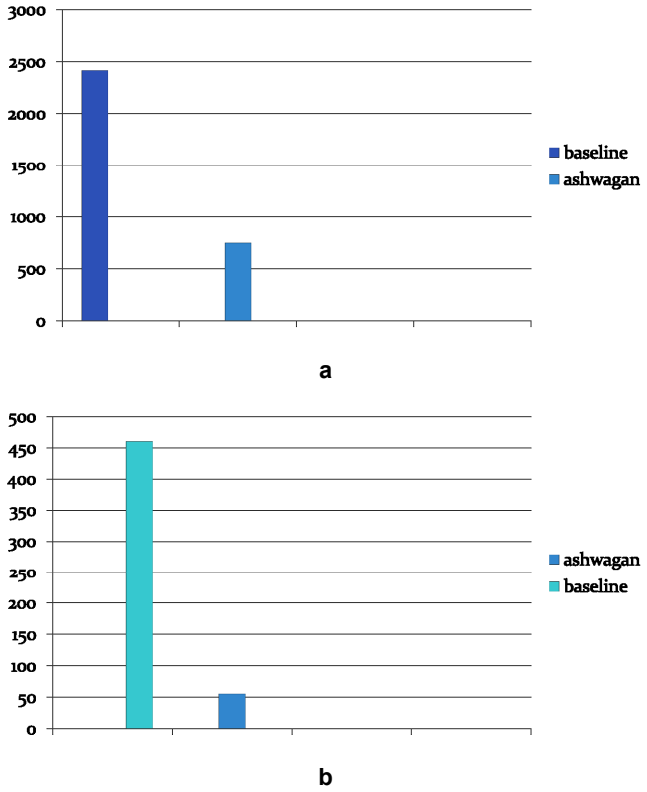


Figure 7: a. Response of patient's serum corticosterone (ng/dl) to Ashwagandha 400 mg twice daily; ashwagan indicates on Ashwagandha.

b. Response of patient's serum 17-OH-pregnenolone (ng/dl) to Ashwagamdha 400 mg twice daily; ashwagan indicates on Ashwagandha.

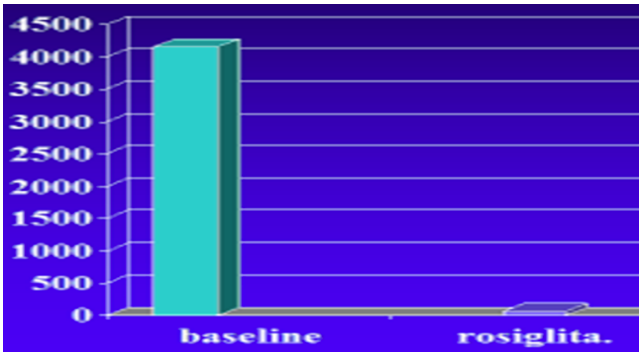


Figure 8: Response of a male, 43 year old patient's serum 17-OH-progesterone (ng/dl) to rosiglitazone 4 mg twice daily. The patient had T2DM and acanthosis nigricans. Rosiglita indicates on rosiglitazone.

We have also reported biochemical and clinical improvement in NCAH patients treated with the PPAR-γ agonist, insulin sensitizer, rosiglitazone [71]. One

example of such an effect in a patient with type 2 diabetes and non-classic 21-hydroxylase deficiency is shown in Figure **8** below, where the response occurred within 24 hours of starting rosiglitazone.

In a patient with non-classic 21-hydroxylase deficiency, who presented with primary infertility and secondary amenorrhea, as shown in Figure **9**, insulin sensitizer therapy with metformin and pioglitazone was more effective than standard therapy with cortisone acetate and fludrocortisone.

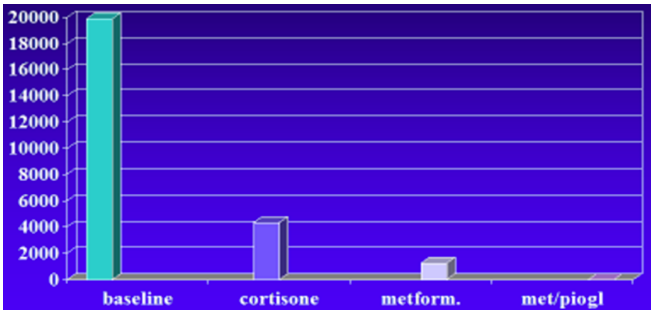
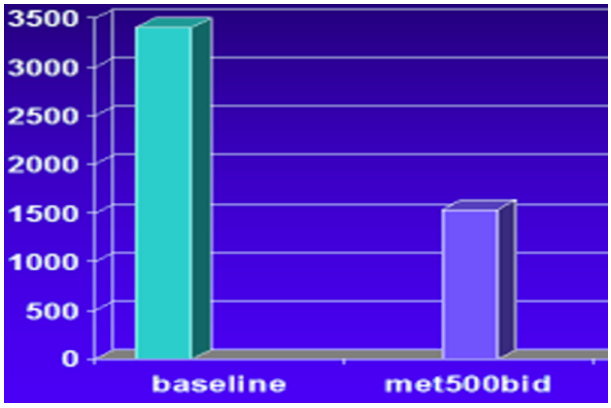


Figure 9: Response of patient's serum 17-OH-progesterone (ng/dl) to cortisone acetate+fludrocortisone 2nd column from left, metformin alone 1 g 2x/day 3rd column from left, and metformin 1 g 2x/day+pioglitazone 15 mg daily 4th column from left.

Classic Congenital Adrenal Hyperplasia is also Associated with Insulin Resistance

Atabek *et al.* [72] and Charmandari *et al*. [73] have reported than insulin resistance is also a feature of both classic 21-hydroxylase deficiency and classic 11-hydroxylase deficiency. We have reported that classic 21-hydroxylase deficiency may be responsive to the insulin sensitizer metformin [74] in a 17 year old patient with secondary amenorrhea and hirsutism who still had very elevated serum 17-OH-progesterone and testosterone levels despite being on standard therapy with hydrocortisone and fludrocortisone (Figures **10a** and **10b**).



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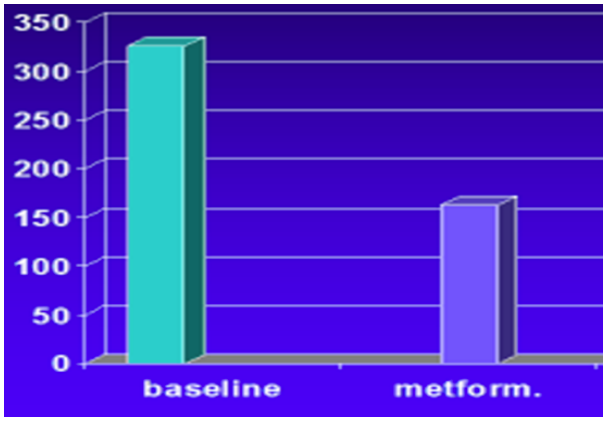

b

Figure 10: a. Response of serum 17-OH-progesterone (ng/dl) to the addition of metformin 500 mg 2x daily to standard therapy with hydrocortisone and fludrocortisone on a patient with classic 21-hydroxylase deficiency. Met500bid indicates metformin 500 mg twice daily.

b. Response of serum total testosterone to the addition of metformin 500 mg twice daily to standard therapy with hydrocortisone and fludrocortisone in a patient with classic 21-hydroxylase deficiency. Metform indicates metformin.

Drugs that cause Insulin Resistance may Increase the Biochemical and Clinical Expression of NCAH, while the Insulin Sensitizers Metformin and Rosiglitazone may Ameliorate it

We have reported that classical and atypical anti-psychotic medications as well as valproic acid, all known to cause insulin resistance, also have an endocrine disrupting effect on adrenal steroidogenesis, which may be reversed with the insulin sensitizers metformin and rosiglitazone [75], Figures **11a-11c**. In this series modified Koch's postulates were fulfilled. The agents known to cause insulin resistance induced NCAH and the insulin sensitizers reversed it.

While some of the observed benefits of Vitamin D repletion in classic CAH and NCAH are likely due to a reduction in insulin resistance, the abundance of VDRs in the adrenal cortex suggests that Vitamin D may also have a direct regulatory effect on adrenal steroidogenesis. This effect may be either stimulatory or inhibitory (adaptogenic) depending upon circumstances [76].

Possible Role of Contiguous Gene Deletion Syndrome in the Pathogenesis of Confluent 21-Hydroxylase Deficiency and Connective Tissue Disorders

In the case of 21-hydroxylase deficiency, approximately 9% of affected individuals have a contiguous gene deletion syndrome involving both 21-

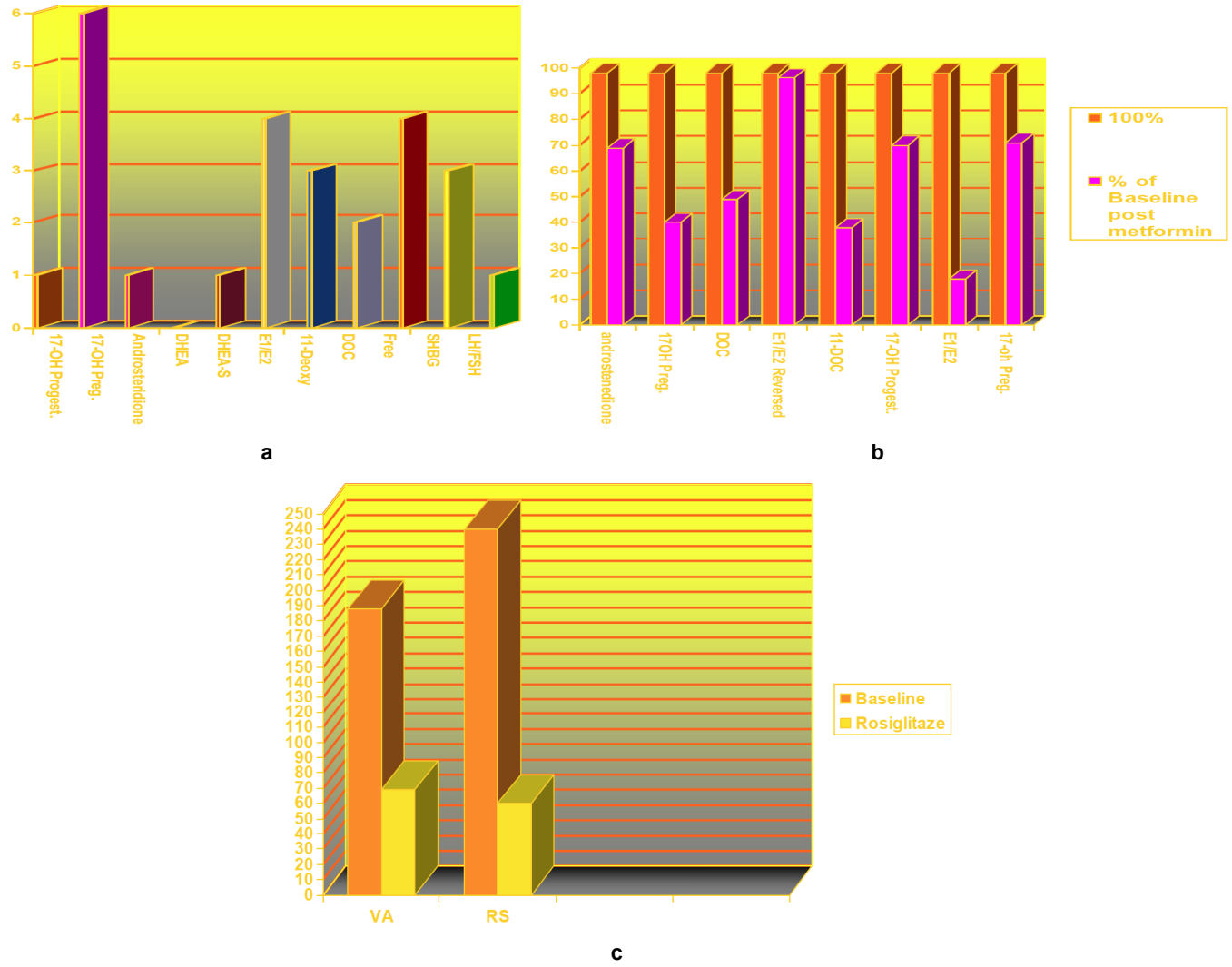

Figure 11: a. Number of Patients with Elevated Steroid Metabolites or Low SHBG or Reversed LH/FSH; left to right 17-OH-progesterone, 17-OH-pregnenolone, androstenedione, DHEA, DHEA-S, estrone/estradiol ratio, 11-deoxycortisol, deoxycorticosterone, free testosterone, SHBG, LH/FSH ratio.

b. Effect of Metformin on Elevated Serum Steroid Metabolites in Individual Patients. (Represented as % of Baseline); left to right androstenedione, 17-OH-pregnenolone, deoxycorticosterone, estrone/estradiol ratio, 11-deoxycortisol, 17-OH-progesterone, estrone/estradiol ratio, 17-OH-pregnenolone.

c. Effect of Rosiglitazone on Elevated Baseline Serum 11- Deoxycortisol Level (ng/dl) in 2 patients with Psychotropic-Induced Non-classic 11-Hydroxylase Deficiency.

hydroxylase and tenascin XB, a collagen gene on chromosome 6. This opens up the possibility that numerous coexistent mutations of 21-hydroxylase and tenascin XB could arise with patients having both CAH or NCAH and a collagen disorder [77-78]. An abnormal tenascin XB segment could potentially serve as an epitope for the development of an autoimmune process directed at collagen.

The fact that these patients often have non-rheumatic cardiac valvular abnormalities related to the tenascin XB mutations is consistent with our earlier report of patients with such valvular abnormalities having NCAH, although such valvular abnormalities could also be related to disordered adrenal ouabain synthesis [79-80].

Possible Role of the Location of the 21-Hydroxylase Gene in the Association of 21-Hydroxylase Deficiency with Autoimmune Disorders

The location of the 21-hydroxylase gene within the HLA locus on chromosome 6, where a host of gene polymorphisms predisposing to autoimmune disorders reside, predicts that 21-hydroxylase deficiency will often coexist with autoimmune disorders.

Adrenal Insufficiency may be Partial and Biochemically and Clinically Indistiguishable from Classic or Non-Classic Adrenal Hyperplasia

A significant number of patients with partial loss of adrenal function (limited adrenocortical reserve) appear well, but experience adrenal crisis when under physiologic stress (eg, surgery, infection, burns, critical illness). Shock and fever may be the only signs [81]. In autoimmune hypoparathyroidism and autoimmune polyglandular syndrome antibodies vs 21-hydroxylase are typically present.

Some of these patients may have only partial forms of adrenal insufficiency, biochemically and clinically indistinguishable from patients with NCAH, accompanied by other autoimmune disorders [82]. Autoimmune responses to other adrenocortical enzymes, eg side chain cleavage enzyme have also been reported in patients with autoimmune Addison's disease [83]. The existence of partial forms of adrenal insufficiency was predicted by none other than Dr. Thomas Addison, himself [84].

Insulin Sensitization has been Proposed as a Therapeutic Strategy in the Treatment of Autoimmune Disorders

Metformin has been among the insulin-sensitizing approaches proposed to treat autoimmune disorders [85]. Autoimmune disorders are characterized by the presence of antibodies directed against specific organs. Some common traits of autoimmune disorders are chronic inflammation caused by inflammatory mediators, and disorders of redox processes. The pathogenesis of autoimmune diseases is still unknown. Treatment is based only on relieving the symptoms and improving the quality of patients' lives. Metformin has qualities which are desirable in autoimmune disease therapy, including anti-inflammatory/antioxidant effects, and an ability to regenerate vascular endothelium.

Treatment with metformin and pioglitazone has beneficial anti-inflammatory effects in patients with Multiple Sclerosis and Metabolic Syndrome [86]. Very recently, systemic usage of metformin for psoriasis has shown promising results [87]. A proof-of-concept trial of metformin add-on treatment for mild or moderate SLE resulted in decreases in clinical flares, prednisone exposure, and body weight [88].

Metformin has been reported to have a beneficial effect in patients with interferon-induced thyroiditis and, to a lesser extent, in patients with Hashimoto's thyroiditis [89]. Apart from reducing plasma glucose, homeostasis model assessment insulin resistance (HOMA-IR) and glycated hemoglobin, metformin decreased serum levels of thyrotropin. Circulating levels of thyroid hormones, prolactin and insulin-like growth factor-1 (IGF-1) remained at a similar level throughout the study. The effect of metformin on serum thyrotropin was stronger in patients with interferon-induced thyroiditis than in patients with Hashimoto's thyroiditis, and correlated with its impact on insulin sensitivity.

In addition to the original use, clinical applications for the therapy of several specific inflammatory diseases such as inflammatory bowel disease and rheumatoid arthritis are expected, because many reports indicated the anti-inflammatory effects of PPAR-gamma agonists on various animal disease models. In fact, several drugs and compounds in this class are used or are undergoing clinical trials for the therapy of rheumatoid arthritis, ulcerative colitis, and other inflammation-related diseases [90].

PPARgamma has been recently described as being a gene of susceptibility for Inflammatory Bowel Diseases (IBD) as has the NOD2/CARD15 gene. Inflammatory bowel diseases are pathologies due to an abnormal immune response, in genetically predisposed patients+ to the bacteria of the intestinal flora. PPARgamma, known for its significant role in adipogenesis, is strongly expressed by the epithelial cells of the colon mucosa. PPARgamma is implicated in the regulation of inflammation. Indeed, agonists of this nuclear receptor decrease strongly the intensity of inflammation during experimental colitis induced by chemical agents. A deficit of PPARgamma in patients with ulcerative colitis has been highlighted, that could, in part, explain the acute inflammation. In addition, bacteria, including those of the commensal flora, are able to regulate PPARgamma. Toll Like Receptor-4 (TLR-4), responsible for the recognition of bacterial motif as lipopolysaccharide (LPS), is implicated in PPARgamma regulation and its anti-inflammatory properties. All these arguments make of PPARgamma a very interesting therapeutic target for the treatment of IBD [91].

Addition of pioglitazone to RA standard of care significantly improves aortic elasticity and decreases inflammation and disease activity with minimal safety issues [92].

After substantial weight loss from bariatric surgery, RA patients had lower disease activity, decreased

serum inflammatory markers, and less RA-related medication use. Weight loss may be an important nonpharmacologic strategy to reduce RA disease activity. However, other factors, such as improved efficacy of medications, improved physical activity, and metabolic changes, may also have contributed to these postsurgical improvements [93]. Long-term weight loss in patients with psoriasis has long-lasting positive effects on the severity of psoriasis [94].

The findings of a recent study suggest that the Ayurvedic, insulin-sensitizing treatment (Ashwagandha powder and Sidh Makardhwaj) has a potential to be used for the treatment of rheumatoid arthritis. However, due to small sample size, short duration, non-randomization, and lack of a control group as study limitations, further studies need to be done to confirm these findings [95].

Recent studies have shown that curcumin ameliorates multiple sclerosis, rheumatoid arthritis, psoriasis, and inflammatory bowel disease in human or animal models. Curcumin inhibits these autoimmune diseases by regulating inflammatory cytokines such as IL-1beta, IL-6, IL-12, TNF-alpha and interferon-gamma (IFN-γ) and associated JAK-STAT, AP-1, and NF-kappa B signaling pathways in immune cells [96]. Many of these cytokines and pathways are involved in the pathogenesis of insulin resistance as well [97].

Many insulin sensitizing interventions,eg metformin, bariatric surgery, dipeptyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 (GLP-1) agonists affect the microbiome [98, 99]. In a general way, the intestinal microbiome characteristic of patients with autoimmune disorders resembles that of patients with the metabolic (insulin resistance) syndrome-that is a lower total bacterial population with less bacterial species diversity.

SUMMARY

We have reviewed evidence for the role of insulin resistance in both congenital adrenal hyperplasia (CAH) and autoimmune disorders and shown that CAH is remarkably prevalent in patients with a variety of autoimmune disorders. Further, the intestinal microbiome is remarkably similar in patients with insulin resistance and those with autoimmune disorders, showing a decreased and less diverse bacterial population. We have also reviewed evidence that insulin-sensitizing interventions, eg weight loss+exercise, bariatric surgery, metformin, thiazolidinediones, Vitamin D repletion, GLP-1 receptor agonists, and Ashwagandha root typically result in clinical improvement and biochemical remission in patients with CAH and NCAH. Similarly, insulin sensitizing interventions including weight loss, bariatric surgery, Vitamin D repletion, metformin, pioglitazone, and curcumin (a naturally occurring antioxidant and TNF-α inhibitor) have been reported to prevent or ameliorate a number of autoimmune disorders. Change to a more plant-based diet, exercise and many of the aforementioned insulin-sensitizing interventions also result in changes in the intestinal biome associated with a leaner, less inflammatory phenotype. We are not surprised to learn that autoimmunity and insulin resistance share a number of inflammatory cytokines, eg TNF-α and IL-6 and common pathways of expression such as MAP kinase and JAK/STAT.

The coming decade will see us connecting more of the dots in this complex, reciprocating series of interactions, which may also have implications for the prevention and treatment of disorders as seemingly diverse as cancer and chronic kidney disease as well.

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