

# Autoimmunity, Non-Classic Adrenal Hyperplasia, Insulin Resistance, 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*

## NON-CLASSIC ADRENAL HYPERPLASIA AND TYPE 2 DIABETES

Beginning with our observations in the 1990s that many patients with Type 2 diabetes (T2DM) have clinical signs and symptoms of hyperandrogenism such as hirsutism, male pattern alopecia, acne, menstrual irregularity, and infertility we went on to systematically evaluate these patients for hyperandrogenism and found that, with the notable exception of patients whose Type 2 diabetes developed in the setting of chronic Hepatitis C and no known family history of Type 2 diabetes, all had evidence of non-classic adrenal hyperplasia (NCAH) [1-4]. Subsequently, we found this relationship to be true even in those T2DM patients without clinical features of hyperandrogenism.

## NON-CLASSIC ADRENAL HYPERPLASIA AND AUTOIMMUNE DISORDERS

Having demonstrated that T2DM is consistently associated with NCAH we began to wonder if Type 1 diabetes (T1DM) was also associated with NCAH. Once again, we found that all of our T1DM patients had evidence of NCAH [5]. We now began to speculate whether NCAH might be a feature of autoimmune disorders in general. It should be remembered that at this time, T2DM was not considered to have autoimmunity as part of its pathogenesis (see Dr. Banerji's lecture), although its association with certain autoimmune disorders, eg psoriasis and vitiligo, was widely recognized. Currently, it is recognized that autoimmunity contributes to the pathogenesis of T2DM [6].

We systematically screened our patients with a number of autoimmune disorders including: Hashimoto's thyroiditis, Graves' Disease, vitiligo,

psoriasis, and rheumatoid arthritis [7-11] for NCAH and found that NCAH was virtually universally present in these patients. Although we have seen only very small numbers of patients with other autoimmune disorders, the few that we have seen with systemic lupus erythematosus, celiac disease, and inflammatory bowel disease all seem to have NCAH.

## POSSIBLE REASONS FOR THE HIGH PREVALENCE OF NCAH IN PATIENTS WITH AUTOIMMUNE DISORDERS

Our reported findings raise the question of why NCAH should be so prevalent in patients with autoimmunity. Several possible explanations are possible.

First, let us consider that the hormone cortisol and its glucocorticoid analogues, eg prednisone, are standard therapies for many autoimmune disorders. In NCAH there is always a mild, chronic deficit of cortisol. Could a mild, yet persistent, deficit of an anti-autoimmune hormone eventually result in the expression of an autoimmune disorder in those who are genetically or epigenetically pre-disposed to such disorders?

Next, let us consider the location of the 21-hydroxylase gene, the gene most commonly associated with both NCAH and classic congenital hyperplasia (CAH). It is located in chromosome 6 within the major histocompatibility (MHC) locus and contiguous with the tenascin X gene. Tenascin X is a collagen protein and, as such, is a component of connective tissue. Both the hyperelasticity (Ehlers-Danlos) syndrome and cardiac valvulopathies have been reported in patients with contiguous mutations in the 21-hydroxylase and tenascin XB genes [12]. It is not hard to conceive that a mutant tenascin XB protein might be more difficult for the immune system to recognize as a self-protein to be tolerated, thus facilitating a humoral and cellular immune response against connective tissue containing the abnormal

\*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

collagen. Similarly, an abnormal, mutant 21-hydroxylase protein might not be recognized as self and facilitate the development of autoimmune adrenal insufficiency (Addison's disease). This would also be true for mutant forms of other adrenal steroidogenic proteins such as 11-hydroxylase.

In addition to proximity to the tenascin XB gene, the 21-hydroxylase gene is also in close proximity to numerous genes within the MHC locus, polymorphisms of which are highly associated with autoimmune disorders, including Autoimmune Polyglandular Syndrome 2. This close proximity allows for frequent simultaneous polymorphisms in both MHC genes and the 21-hydroxylase gene.

The gene for the 4th component of complement (C4) is also located very close to the 21-hydroxylase locus. Complement is an integral part of the innate immune system. Genetic deficiency of any early component of the classical pathway (C1q, C1r/s, C2, C4, and C3) is associated with autoimmune diseases due to the failure of clearance of immune complexes (IC) and apoptotic materials, and the impairment of normal humoral response. Thus, mutations of both the 21-hydroxylase and C4 genes could easily occur simultaneously, resulting in both NCAH and an autoimmune disorder [12-13].

### Insulin Resistance in NCAH

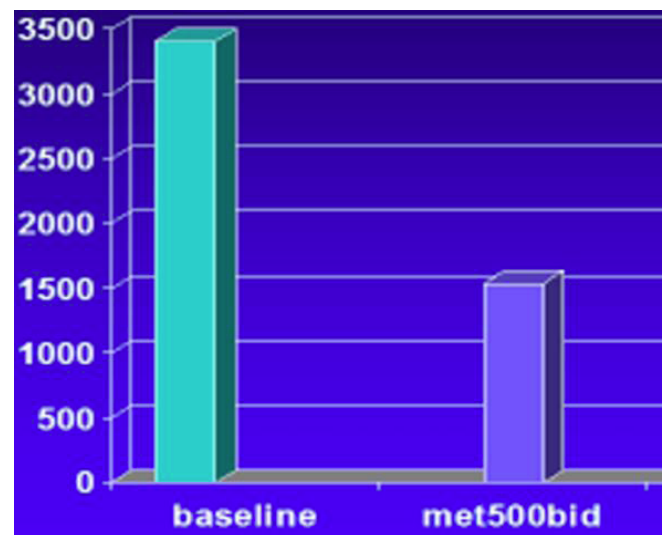
As insulin sensitizers became available, first metformin and then the thiazolidinediones, we began to notice that many of our patients with T2DM and NCAH were experiencing improvements in their alopecia, hirsutism, acne, menstrual irregularity, and infertility after starting these agents. We began to wonder whether IR was necessary for NCAH to be expressed. When we retested our diabetic and prediabetic patients with NCAH while taking metformin +/- troglitazone we found that in every instance the initially elevated steroid metabolite eg 17-OH-progesterone, had declined- in most cases, back into the normal range [2,3, 14-15].

Sparse reports began to appear in the literature [16-17] from Dr. New's group at New York Hospital and Dr. Saygili's group in Turkey that IR was a regular feature of patients with NCAH. However, neither group suggested targeting the IR as a means of treating the NCAH.

### Insulin Resistance in Classic CAH

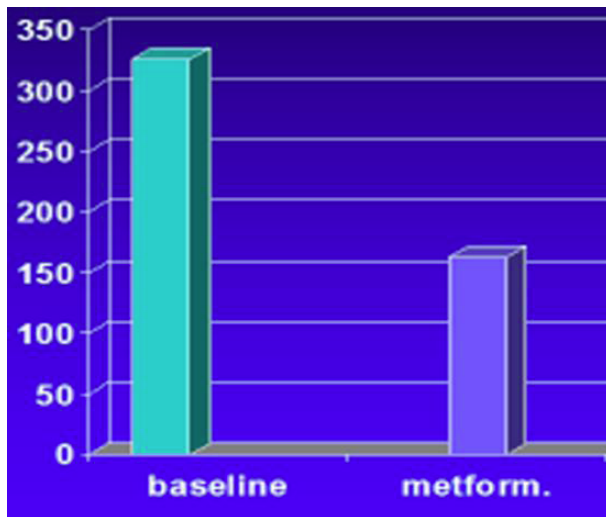
As adult endocrinologists, we saw few patients with classic CAH, as they tend to remain under the care of

their pediatric endocrinologists until well into adulthood. Nevertheless, we wondered whether IR was also a characteristic of patients with classic CAH as well. An article by Charmandari *et al.* from Dr. Chrousos' group at the National Institutes of Health [18] and a case report from Turkey [19] went a long way toward answering this crucial question. They reported that 102 patients with classic CAH, 100 with 21-hydroxylase deficiency and 2 patients with 11-hydroxylase deficiency all had IR, independently of their glucocorticoid therapy. Again, while the authors recognized this as a problem which could increase their patients' risk of developing complications of IR such as metabolic syndrome and T2DM, they did not raise the possibility that addressing the IR might ameliorate the classic CAH. This possibility would wait until our colleague, Dr. Levon Agdere, a pediatric endocrinologist, called us to say that he was seeing a 17 year old female patient with classic 21-hydroxylase deficiency, who, despite receiving optimal traditional treatment with cortisone acetate and fludrocortisone, had recently developed amenorrhea and hirsutism. The serum 17-OH-progesterone was still very high around 3500 ng/dl and the serum testosterone was still in the adult male range (>300) (see Figures 1,2).



**Figure 1:** Change in Serum 17-OH-progesterone (ng/dl) after metformin 500 mg twice daily (met500bid) was added to standard steroid treatment in a patient with classic 21-hydroxylase deficiency.

Most authorities caution against attempting to normalize the levels of 17-OH-progesterone and androgens in these patients due to glucocorticoid side effect such as hypertension, hyperglycemia, bone loss, hypokalemia, affective changes, and weight gain when supra-physiologic doses are used.



**Figure 2:** Change in Serum total testosterone (ng/dl) after metformin 500 mg twice daily (met500bid) was added to standard steroid treatment in a patient with classic 21-hydroxylase deficiency.

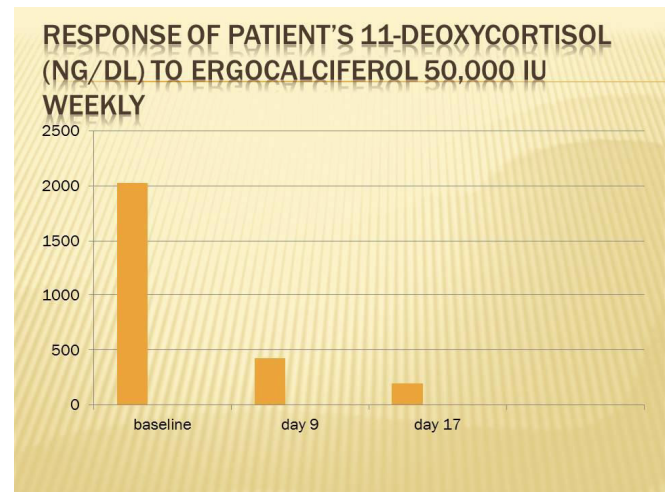
### TARGETING INSULIN RESISTANCE IN CLASSIC CAH

We agreed, after obtaining informed consent from the patient and her parents, to continue her on her regimen of cortisone acetate + fludrocortisone and to add the insulin sensitizing, anti-diabetic agent, metformin, starting at 500 mg twice daily. When she returned to Dr. Adgere's clinic 3 months later she had resumed monthly menses and stated that she had to remove to remove unwanted hair less often. Her repeat serum 17-OH-progesterone and total testosterone levels had both declined by about 50% [20]. She was offered the opportunity to up-titrate the dosage of metformin and possibly add a second insulin sensitizer in an attempt to normalize her serum 17-OH-progesterone and testosterone concentrations and gradually wean her off steroids. The patient, however, thanked Dr. Agdere for the improvement she had experienced up to this point and declined any further change in her therapy. Thus, to date, we are unable to say definitively whether or not insulin sensitizers can eliminate the need for steroids in classic 21-hydroxylase deficiency as they do in NCAH.

On the other hand, we have been able to demonstrate that in a patient with both classic CAH due to 11-hydroxylase deficiency and Vitamin D deficiency repletion of Vitamin D, using ergocalciferol 50,000 IU weekly, his serum 11-deoxycortisol was normalized without using steroids [21] (Figure 3).

### TARGETING INSULIN RESISTANCE IN NCAH

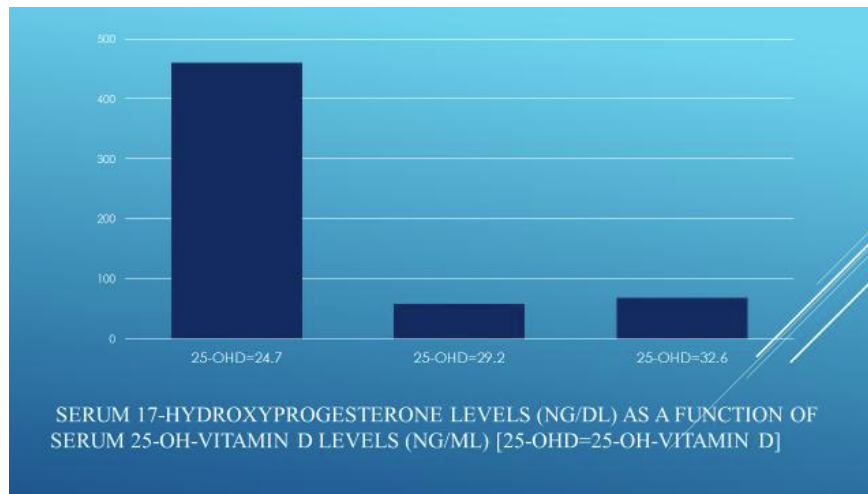
Another patient we were consulted on to help improve his glycemic control as his surgical team



**Figure 3:** Response of serum 11-deoxycortisol (ng/dl) to Vitamin D repletion in a patient with classic 11-hydroxylase deficiency.

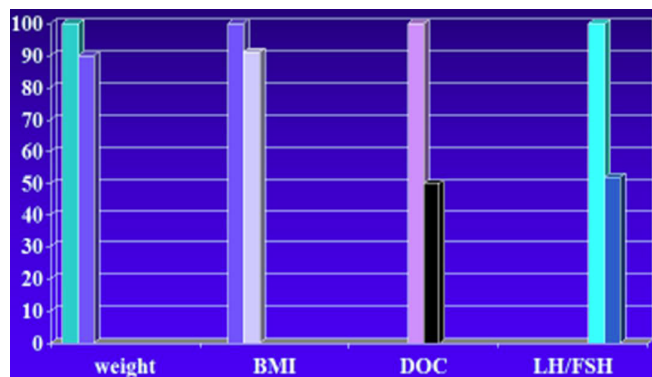
attended to his serious lower extremity infection. Endocrine investigation revealed that the patient, a middle-aged physician from Jamaica, had both non-classic 21-hydroxylase deficiency and Vitamin D insufficiency. Given his serious infection we could not use metformin to treat either his diabetes or his NCAH because of the risk of precipitating lactic acidosis. Ergocalciferol 50,000 IU every 2 weeks was begun. Within 2 weeks his serum 25-OH-Vitamin D had nearly normalized and his serum 17-OH-progesterone had normalized [22] (Figure 4).

Weight loss is another way that IR may be reduced. Is weight loss a viable way to treat NCAH as it is in polycystic ovarian syndrome (PCOS)? This question was partially answered by 2 of our patients who both had hirsutism, Class 1 obesity, and non-classic aldosterone synthase deficiency. This form of NCAH was first reported by E Philip Osehobo and myself in 1998 [23]. I told the first of these 2 patients that the most logical means of treating her aldosterone synthase deficiency was with the synthetic mineralocorticoid, fludrocortisone. She said that she felt that if she adopted a healthier lifestyle her condition would improve. She asked me for a referral to a nutritionist and joined a gym, which she did and attended regularly. When she returned 3 months later she had lost 10% of both her body weight and her BMI. She reported that she had to remove facial and body hair less frequently. Her previously elevated serum deoxycorticosterone fell by 50%, into well within the normal range, and her previously elevated LH/FSH ratio also normalized [24]. Following this favorable outcome, the same therapeutic approach was used in another patient with non-classic aldosterone synthase



**Figure 4:** Response of serum 17-OH-progesterone (ng/dl) to vitamin D repletion in a patient with non-classic 21-hydroxylase deficiency.

deficiency with comparable results. Pooled data for these 2 patients is shown in Figure 5.



**Figure 5:** Response of 2 patients' weight, body mass index (BMI), serum deoxycorticosterone (DOC) (ng/dl), & luteinizing hormone/follicle stimulating hormone (LH/FSH) to lifestyle changes.

Percent Changes with Weight Loss.

After troglitazone was withdrawn from the market due to its rare, idiosyncratic, but very serious liver toxicity, two other thiazolidinediones that did not have this issue, were released, rosiglitazone and pioglitazone. NCAH patients that we treated with these agents responded similarly to those that we had treated earlier with troglitazone, again paralleling the experience that was being reported using these agents in PCOS patients.

#### **DRUGS THAT CAUSE IR CAUSE EXPRESSION OF NCAH, A FORM OF ENDOCRINE DISRUPTION**

If IR is a constant feature of both NCAH and classic CAH it is logical to ask whether medications known to cause IR can induce the expression of NCAH and whether interventions that reduce IR can ameliorate

such NCAH. One such group of drugs is the classic and atypical anti-psychotic drugs. Another frequently prescribed psychotropic agent is valproic acid. We screened 27 consecutive psychiatric in-patients who were taking one or more of these agents who we had been called to see for endocrine consultations. 27/27 of these patients had biochemical NCAH, many with clinical features such as hirsutism, acne, alopecia, and irregular menses.

Two other classes of drugs which also cause IR are the protease inhibitors and the nucleoside analogues, both used anti-retroviral therapy. We screened 11 HIV+ve patients who were taking drugs from one or both of these classes and found that 11/11 had NCAH [25]. We did not, however, have the opportunity to treat this group of patients with insulin sensitizers.

#### **INSULIN SENSITIZERS REVERSE DRUG-INDUCED NCAH EXPRESSION**

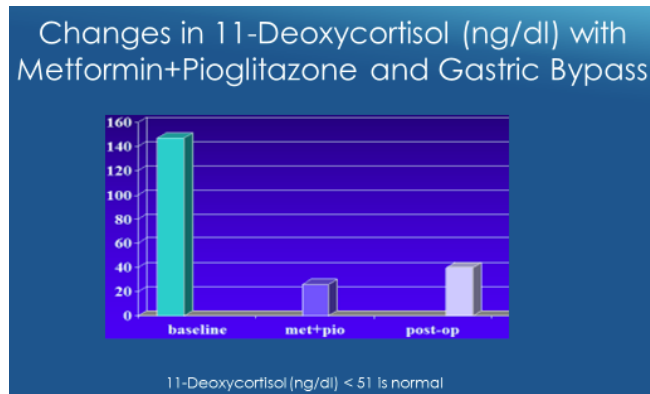
When treated with insulin sensitizers-metformin alone or with rosiglitazone or rosiglitazone alone 27/27 patients experienced biochemical normalization [15].

#### **EFFECT OF BARIATRIC SURGERY IN NCAH**

While lifestyle changes can result in a reduction in IR and amelioration of both NCAH and PCOS, it is known that bariatric surgery can result in even more rapid and dramatic improvements in insulin sensitivity. When one of our patients with morbid obesity, T2DM, hypertension, dyslipidemia, and hirsutism associated with non-classic 11-hydroxylase deficiency opted to undergo Roux-en-Y gastric bypass surgery we fully expected amelioration of her first four issues. Based on



our previous experience with this patient using a combination of the insulin sensitizers, metformin and pioglitazone, which normalized her serum 11-deoxycortisol we predicted the same would occur following bariatric surgery. When we saw her 5 weeks after her surgery she had lost 7 kg, she was euglycemic, normolipidemic, and normotensive without medication and her serum 11-deoxycortisol remained normal [26] (Figure 6).



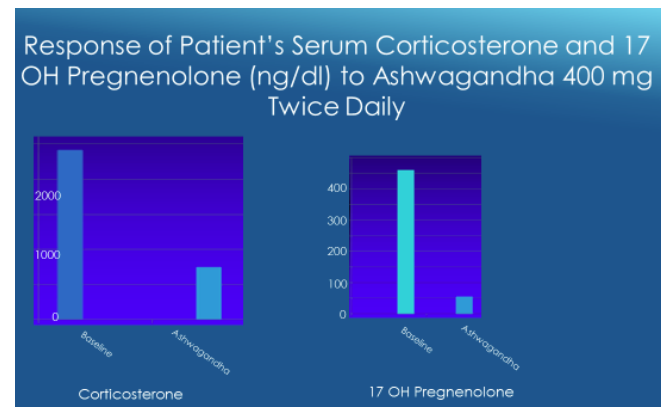
**Figure 6:** Changes in serum 11-deoxycortisol (ng/dl) with metformin+pioglitazone (met+pio) and 5 weeks Post-Roux-en-Y gastric bypass (post-op) off medication.

Two other patients afforded us the opportunity to explore a complementary treatment for NCAH. The first patient, a 57 year old woman, complained of excessive scalp hair loss, despite appearing to have a luxuriant head of hair. She then showed me a photograph on her smart phone of how her pillow looked when she got up on a recent morning—it was covered with hair. Investigation revealed that she had both non-classic 3-beta-hydroxysteroid dehydrogenase deficiency and aldosterone synthase deficiency. Initially she was treated with pioglitazone 15 mg daily. At her subsequent visit 3 months later her daily hair loss was much less, which she documented with another smart phone photo. In addition, her previously very elevated levels of 17-OH-pregnenolone and corticosterone had normalized. Despite being very pleased with the results she had achieved, she elected not to continue taking pioglitazone because of potential risks of osteoporosis, bladder cancer, and weight gain. I offered her a prescription for the insulin sensitizer metformin, noting that its use was not associated with any of these side effects, as an alternative. When she returned 3 months later, she was still very pleased that her rate of hair loss had not increased and I was also pleased to note that her serum concentrations of both 17-OH-pregnenolone and corticosterone remained normal. I immediately attributed this therapeutic success to

metformin. She looked at me rather sheepishly and then told me that she filled the metformin prescription at her pharmacy, but had never actually started to take it. Two days after her previous visit with me she had been watching Dr. Oz, a popular, nationally syndicated television program about health issues.

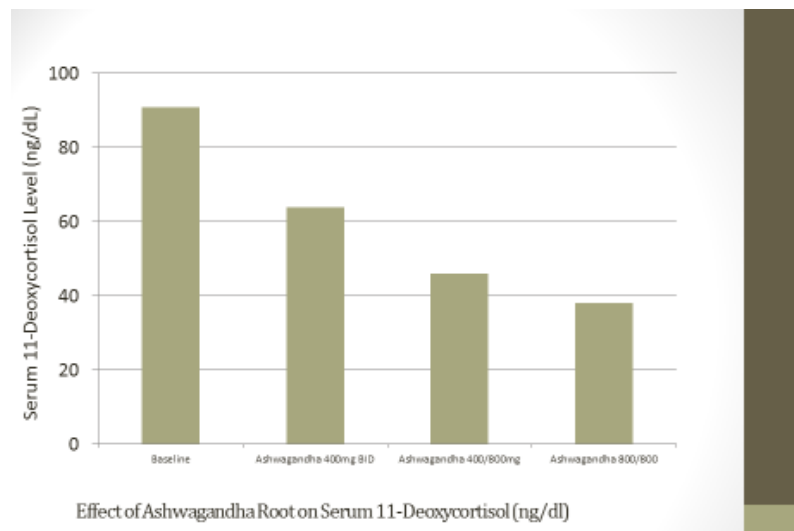
During this program Dr. Oz discussed some of the attributes of the Aryurvedic herb, Ashwagandha (*Withania somnifera*) including it being a general tonic and an adaptogen (Adaptogens or adaptogenic substances are used in herbal medicine for the claimed stabilization of physiological processes and promotion of homeostasis). He did not claim any specific benefit insofar as hair loss was concerned.

She then purchased this product from the recommended manufacturer and started to take it at the dose recommended by Dr. Oz, 400 mg twice daily [27] (Figure 7).

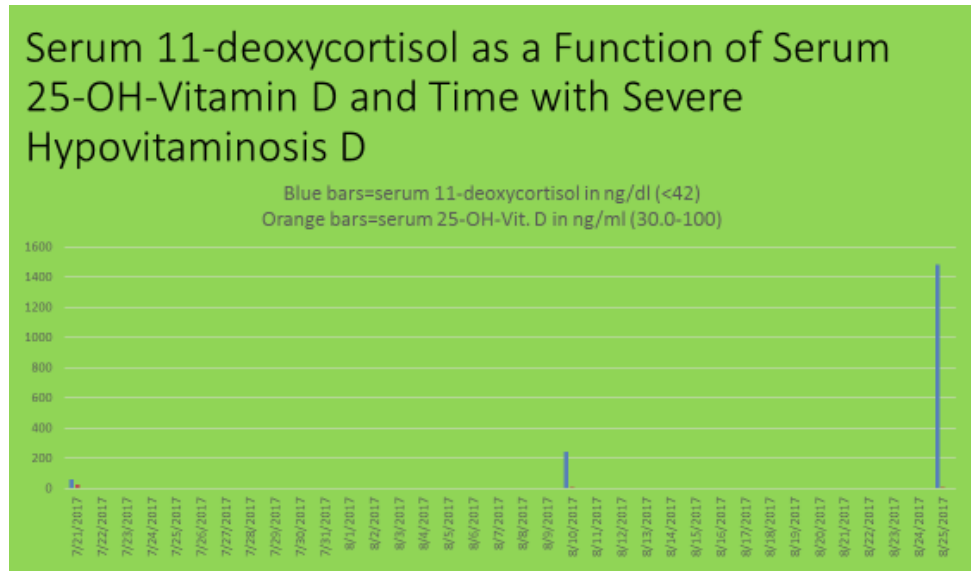


**Figure 7:** Response of a patient with both non-classic aldosterone synthase deficiency and non-classic 3- $\beta$ -ol-dehydrogenase deficiency to Ashwagandha root 400 mg 2x/day.

After this patient's gratifying response to Ashwagandha we recommended it to a second patient, an 80 year old woman who was complaining of thinning scalp hair and acne, in whom recent investigation revealed non-classic 11-hydroxylase deficiency to be the likely cause of her complaints. Metformin was not an option because this patient had chronic kidney disease stage 3b. The patient had indicated her strong preference for "natural" treatment of her NCAH. We initiated treatment with the same dose of Ashwagandha we had used successfully with the previous patient, 400 mg twice/day. While her acne and hair loss noticeably improved on this dose and her serum 11-deoxycortisol improved considerably, her serum 11-deoxycortisol did not normalize until a dose of 800 mg twice/day was reached [28] (Figure 8).



**Figure 8:** Dose-related response of serum 11-deoxycortisol to Ashwagandha root in a patient with non-classic 11-hydroxylase deficiency.

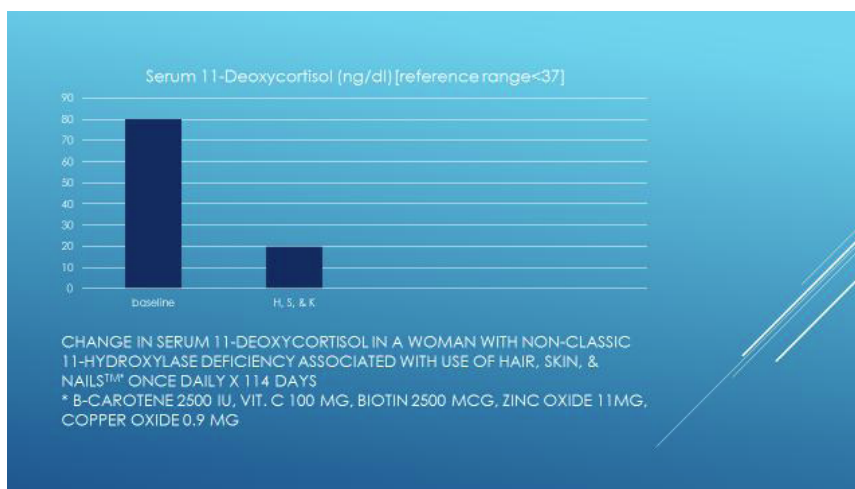


**Figure 9:** Increase in serum 11-deoxycortisol with worsening and prolonged hypovitaminosis D in a patient with non-classic 11-hydroxylase deficiency.

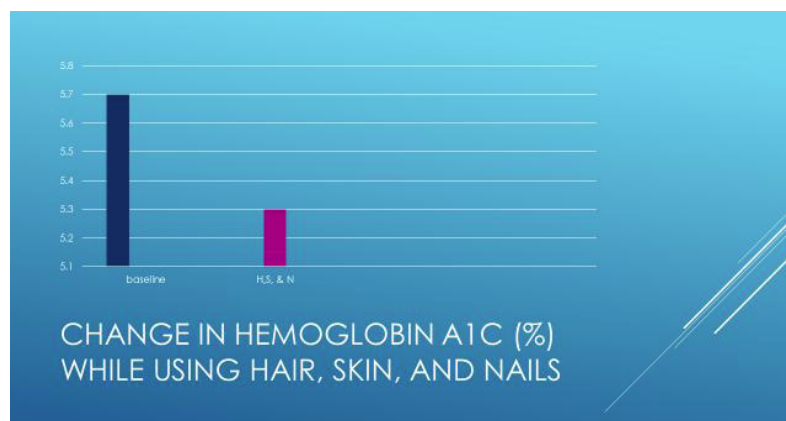
After having demonstrated that Vitamin D repletion in Vitamin D deficient/insufficient people often ameliorates NCAH/ CAH a patient with hypovitaminosis D (baseline 25-OH-vitamin D<sub>3</sub>=24.4 ng/ml) and non-classic 11-hydroxylase deficiency (baseline serum 11-deoxycortisol=62 ng/dl) was seen in consultation. He had recently undergone a partial bowel resection and was being fed by total parenteral nutrition (TPN). TPN, being aqueous, does not contain Vitamin D, which is lipid soluble. Hypovitaminosis D was exacerbated by lack of access to any natural or artificial ultraviolet light source. When next sampled, about 2 weeks later he had severe Vitamin D deficiency (10.3 ng/ml) and his serum 11-deoxycortisol had risen impressively to 246

ng/dl. As oral or enteral feeding still had not been initiated, his severe Vitamin D deficiency persisted (12.7 ng/ml) and his serum 11-deoxycortisol rose astronomically (1486 ng/dl) [29] (Figure 9). It had now been demonstrated not only that hypovitaminosis D was frequently encountered in patients with NCAH and CAH and that Vitamin D repletion generally ameliorated both conditions, but that the converse was also true—that worsening and prolonged Vitamin D deficiency is associated with exacerbation of NCAH.

One of our patients with a diagnosis of non-classic 11-hydroxylase deficiency and prediabetes with a chief complaint of thinning scalp hair was prescribed



**Figure 10:** Normalization of serum 11-deoxycortisol with “Hair, Skin, & Nails” (H,S,& K) in a patient with non-classic 11-hydroxylase deficiency and prediabetes.



**Figure 11:** Change in HbA1C with “Hair, Skin, & Nails” (H,S, & K) in a patient with non-classic 11-hydroxylase deficiency and prediabetes.

metformin to address these issues. She only took metformin for 2 days after which she purchased an over the counter preparation called Hair, Skin, and Nails containing beta carotene 2500 IU, Vitamin C 100 mg, biotin 2500 mcg, zinc oxide 11 mg, and copper oxide 0.9 mg for 114 days. When she returned both her serum 11-deoxycortisol and her hemoglobin A1c had normalized (Figures 10-11).

An interesting study from Poland suggests that it may be hyperinsulinemia, which typically is a compensatory accompaniment to IR, rather than IR itself, that may be the critical factor in the expression of NCAH [30]. In this study 4 women with both hypercholesterolemia and non-classic 21-hydroxylase deficiency, who were already taking metformin, were treated with simvastatin for their hypercholesterolemia. Statin drugs are known to reduce serum insulin levels, which is believed to be one the mechanisms for their mildly diabetogenic effect. All 4 patients not only

reduced their serum total and LDL cholesterol and their serum insulin concentrations but they normalized their elevated serum 17-OH-progesterone concentrations as well.

### INSULIN SENSITIZERS AND AUTOIMMUNITY

There is a growing body of literature reporting that interventions known to decrease IR, including metformin [31-35], pioglitazone [32, 36,37,38], weight loss [39], bariatric surgery [40], Ashwagandha [41], and Vitamin D repletion have efficacy in prevention of some and amelioration of a number of autoimmune disorders [42-50]. Curcumins derived from turmeric have both insulin-sensitizing and anti-autoimmune effects [51].

### THE GUT BIOME

There are also broad similarities in the gut biome of people with IR/metabolic syndrome and those with many autoimmune disorders, characterized by a

decrease in both total number and species diversity of organisms. Improvements in insulin sensitivity are associated with increases in species diversity and absolute number of organisms [52]. Conversely, fecal transplants from insulin sensitive individuals to insulin-resistant individuals will restore insulin sensitivity to the latter, however, their biome will revert to IR type unless their lifestyle changes as well, to one characterized by a more plant-based diet and more physical activity [54-55].

What we are seeing are myriad interconnections between insulin resistance/hyperinsulinemia, congenital adrenal hyperplasia, Vitamin D, and the gut biome. These interconnections offer us many potential therapeutic targets to benefit our patients. Single interventions often have a multiplicity of benefits.

## REFERENCES

- [1] Sacerdote AS. Adrenal androgens and NIDDM. *Diabetes Care* 1995; 18(2): 278-9. <https://doi.org/10.2337/diacare.18.2.278b>
- [2] Bahtiyar G, Sacerdote A. Latest Therapeutic Advances in the Treatment of Congenital Adrenal Hyperplasia in Adolescents and Adults. In "Amenorrhea; publisher-Intech.
- [3] Sacerdote A, Bahtiyar G (2015). Treatment of Congenital Adrenal Hyperplasia by Reducing Insulin Resistance and Cysticercosis Induced Polycystic Ovarian Syndrome, *Contemporary Gynecologic Practice*, Prof. Atef Darwish (Ed.), ISBN: 978-953-51-1736- 0, InTech, Available from: <http://www.intechopen.com/books/contemporary-gynecologic-practice/treatment-of-congenital-adrenal-hyperplasia-by-reducinginsulin-resistance-and-cysticercosis-induced>-Published on line 11-2011; published in print 12-2011.
- [4] Sacerdote A. The expanding universe of androgenic disorders; Guest Editorial in *Endocrine Today* 2005; 3(2): 4-7.
- [5] Sacerdote A. Adrenal Hyperandrogenemia in IDDM. Program and Abstracts, 77th Annual Meeting of The Endocrine Society 1995; 545, (poster presentation).
- [6] Itariu BK, Stulnig TM. Autoimmune aspects of type 2 diabetes mellitus - a mini-review. *Gerontology* 2014; 60(3): 189-96. <https://doi.org/10.1159/000356747>
- [7] Sacerdote A. Adrenal Hyperandrogenemia in Graves' Disease. Program and Abstracts, Tenth International Congress of Endocrinology II: 1000, 1996 (poster presentation).
- [8] Sacerdote A. Adrenal Hyperandrogenemia in Hashimoto's Thyroiditis. Program and Abstracts, Tenth International Congress of Endocrinology II: 1000, 1996 (poster presentation).
- [9] Sacerdote A, Li Y. Adrenal Hyperandrogenemia in Psoriasis. Program and Abstracts, 79th Annual Meeting of The Endocrine Society 1997; 310. (poster presentation).
- [10] Sacerdote A. Vitiligo Is Associated with Adrenal Hyperandrogenemia. Program and Abstracts, 80th Annual Meeting of The Endocrine Society 1998; 199, (poster presentation).
- [11] Sacerdote AS, Bahtiyar G, Mejía J. Rheumatoid arthritis is associated with non-classical adrenal hyperplasia. Program and Abstracts, Endo 2007, 89th Annual Meeting of The Endocrine Society 2007; 672, (poster presentation).
- [12] Chen W, Kim MS, Shanbhag S, Arai A, VanRyzin C, McDonnell NB, Merke DP. The phenotypic spectrum of contiguous deletion of CYP21A2 and tenascin XB: quadricuspid aortic valve and other midline defects. *Am J Med Genet A* 2009; 149A(12): 2803-8. <https://doi.org/10.1002/ajmg.a.33092>
- [13] Olaisen B, Teisberg P, Nordhagen R, *et al.* Human complement C4 locus is duplicated on some chromosomes. *Nature* 1979; 279: 736-737. <https://doi.org/10.1038/279736a0>
- [14] Sacerdote A, Weiss K, Polanco H, Fermin E, Hussain S. Atypical and Typical Antipsychotics, Divalproex, and Valproic Acid Use are Associated with Adrenal Hyperandrogenemia. Program and Abstracts, Endo 2004, the 86th Annual Meeting of The Endocrine Society 649, 2004 (poster presentation).
- [15] Bahtiyar G, Weiss K, Sacerdote A. Novel endocrine disrupter effects of anti-psychotic drugs and valproate; Induction of adrenal hyperandrogenism; Reversibility with Insulin Sensitizers. *Endocrine Practice* 2007; 13(6): 601-608. *Am J Med Genet A* 2009; 149A(12): 2803-2808.
- [16] Speiser PW, Serrat J, New MI, Gertner JM Insulin insensitivity in adrenal hyperplasia due to nonclassical steroid 21-hydroxylase deficiency. *J Clin Endocrinol Metab* 1992; 75(6): 1421-4.
- [17] Saygili F, Oge A, Yilmaz C. Hyperinsulinemia and insulin insensitivity in women with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency: the relationship between serum leptin levels and chronic hyperinsulinemia. *Horm Res* 2005; 63(6): 270-4.
- [18] Charmandari E, Weise M, Bornstein SR, Eisenhofer G, Keil MF, Chrousos GP, Merke DP. Children with classic congenital adrenal hyperplasia have elevated serum leptin concentrations and insulin resistance: potential clinical implications. *J Clin Endocrinol Metab* 2002; 87(5): 2114-20. <https://doi.org/10.1210/jcem.87.5.8456>
- [19] Atabek ME, Kurtoglu S, Keskin M. Female pseudohermaphroditism due to classical 21-hydroxylase deficiency and insulin resistance in a girl with Turner syndrome. *Turk J Pediatr* 2005; 47(2): 176-9.
- [20] Bahtiyar G, Weiss K, Sacerdote A. Novel endocrine disrupter effects of classic and atypical antipsychotic agents and divalproex: induction of adrenal hyperandrogenism, reversible with metformin or rosiglitazone. *Endocrine Practice* 2008; 13(6): 601-8. <https://doi.org/10.4158/EP.13.6.601>
- [21] Thomas A, Kalani A, Vincent R, Luis-Lam M, Bahtiyar G, Borensztein A, Quinto E, Sacerdote A. Effect of Vitamin D in a patient with classical adrenal hyperplasia due to 11-hydroxylase deficiency. *J Med Cases* 2013; 4(8): 569-75. <https://doi.org/10.4021/jmc1352w>
- [22] Fenteany G, Inoue T, Bahtiyar G, Sacerdote AS. Association of Vitamin D repletion with normalization of elevated serum 17-OH-progesterone. *Med Cas Rep* 2017; 3: 3.
- [23] Osehobo E, Sacerdote, A. Aldosterone Synthase Deficiency; A Newly Described Variant of Non-Classical Congenital Adrenal Hyperplasia. Program and Abstracts, 81st Annual Meeting of The Endocrine Society, 1999 (poster presentation).
- [24] Sacerdote A. Weight-Dependent Expression of Non-Classical Aldosterone Synthase Deficiency. And Abstracts, Endo-2002, The Endocrine Society's 84th Annual Meeting 2002; 599.
- [25] Sacerdote A, Girgis E, Toossi A, Polanco H, Bahtiyar G. Additional endocrine disrupter effects of highly active anti-retroviral treatment-induction of non-classical adrenal hyperplasia. Program and Abstracts, Endo 2006 88th Annual meeting of The Endocrine Society 202, 2006 (poster presentation).



- [26] Kalani A, Thomas N, Sacerdote A, Bahtiyar G. Roux-en-Y gastric bypass in the treatment of non-classic congenital adrenal hyperplasia due to 11-hydroxylase deficiency. *BMJ Case Rep* 2013; 2013.
- [27] Baby A, Inoue T, Ezeji G, Giunta J, Bahtiyar G, Sacerdote AS. Ashwagandha Root in the Treatment of Non-Classic 11-Hydroxylase Deficiency Program: Abstracts - Orals, Poster Previews, and Posters Session: THR 402-416-Congenital Adrenal Hyperplasia Clinical Thursday, March 5, 2015: 1: 00 PM-3: 00 PM Hall D-F, Adrenal (San Diego Convention Center) Poster Board THR-416.
- [28] Powell D, Inoue T, Bahtiyar G, Fenteany G, Sacerdote A. Treatment of Nonclassic 11-Hydroxylase Deficiency with Ashwagandha Root. *Case Rep Endocrinol* 2017; 2017: 1869560.
- [29] Inoue T, Soni L, Bahlol M, Fenteany G, Bahtiyar G, Sacerdote A. Worsening and Prolonged Hypovitaminosis D is Associated with Biochemical Exacerbation of Non-classic 11-Hydroxylase Deficiency. Presented at Endo 2018, Chicago, IL Mar 17-20, 2018.
- [30] Krysiak R, Kowalcze K, Bednarska-Czerwińska A, Okopień B. The effect of simvastatin on plasma steroid hormone levels in metformin-treated women with non-classic congenital adrenal hyperplasia. *Exp Clin Endocrinol Diabetes* 2016; 124(4): 215-9.  
<https://doi.org/10.1055/s-0035-1569375>
- [31] Tomczynska M, Bijak M, Saluk J. Metformin - The Drug for the Treatment of Autoimmune Diseases; A New Use of a Known Anti-Diabetic Drug. *Curr Top Med Chem* 2016; 16(19): 2223-30.  
<https://doi.org/10.2174/1568026616666160216152324>
- [32] Negrotto L, Farez MF, Correale J. Immunologic effects of metformin and pioglitazone treatment on metabolic syndrome and multiple sclerosis. *JAMA Neurol* 2016; 73(5): 520-8.  
<https://doi.org/10.1001/jamaneurol.2015.4807>
- [33] Bubna AK. Metformin - For the dermatologist. *Indian J Pharmacol* 2016; 48(1): 4-10.  
<https://doi.org/10.4103/0253-7613.174388>
- [34] Wang H, Li T, Chen S, Gu Y, Ye S. Neutrophil Extracellular Trap Mitochondrial DNA and Its Autoantibody in Systemic Lupus Erythematosus and a Proof-of-Concept Trial of Metformin. *Arthritis Rheumatol* 2015; 67(12): 3190-200.  
<https://doi.org/10.1002/art.39296>
- [35] Krysiak R, Szkrobka W, Okopien B. The Effect of Metformin on Hypothalamic-Pituitary-Thyroid Axis Activity in Women with Interferon-Induced Hypothyroidism: A Pilot Study. *Exp Clin Endocrinol Diabetes* 2016; 124(2): 71-6.  
<https://doi.org/10.1055/s-0035-1565207>
- [36] Wada K, Kamisaki Y. [Anti-inflammatory effect of PPAR gamma agonists: basics and clinical applications]. *Nihon Rinsho* 2010; 68(2): 278-83.
- [37] Rousseaux C, Desreumaux P. The peroxisome-proliferator-activated gamma receptor and chronic inflammatory bowel disease (PPARgamma and IBD)]. *J Soc Biol* 2006; 200(2): 121-31.  
<https://doi.org/10.1051/jbio:2006015>
- [38] Malhotra A, Shafiq N, Rajagopalan S, Dogra S, Malhotra S. Thiazolidinediones for plaque psoriasis: a systematic review and meta-analysis. *Evid Based Med* 2012; 17(6): 171-6.  
<https://doi.org/10.1136/ebmed-2011-100388>
- [39] Jensen P, Christensen R, Zachariae C, Geiker NR, Schaadt BK, Stender S, Hansen PR, Astrup A, Skov L. Long-term effects of weight reduction on the severity of psoriasis in a cohort derived from a randomized trial: a prospective observational follow-up study. *Am J Clin Nutr* 2016; 104(2): 259-65.  
<https://doi.org/10.3945/ajcn.115.125849>
- [40] Sparks JA, Halperin F, Karlson JC, Karlson EW, Bermas BL. Impact of Bariatric Surgery on Patients With Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)* 2015; 67(12): 1619-26.  
<https://doi.org/10.1002/acr.22629>
- [41] Kumar G, Srivastava A, Sharma SK, Rao TD, Gupta YK. Efficacy & safety evaluation of Ayurvedic treatment (Ashwagandha powder & Sidh Makardhwaj) in rheumatoid arthritis patients: a pilot prospective study. *Indian J Med Res* 2015; 141(1): 100-6.  
<https://doi.org/10.4103/0971-5916.154510>
- [42] Schwalfenberg GK. Solar Radiation and Vitamin D: Mitigating Environmental Factors in Autoimmune Disease. *Journal of Environmental and Public Health* Volume 2012 (2012), Article ID 619381.  
<https://doi.org/10.1155/2012/619381>
- [43] Agmon-Levin N, Theodor E, Segal RM, Shoenfeld Y. Vitamin D in systemic and organ-specific autoimmune diseases. *Clin Rev Allergy Immunol* 2013; 45(2): 256-66.  
<https://doi.org/10.1007/s12016-012-8342-y>
- [44] Smolders J, Thewissen M, Peelen E, Menheere P, Tervaert JW, Damoiseaux J, Hupperts R. Vitamin D status is positively correlated with regulatory T cell function in patients with multiple sclerosis. Vitamin D status is positively correlated with regulatory T cell function in patients with multiple sclerosis. *PLoS One* 2009; 4(8): e6635.
- [45] Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016 Mar. CADTH Rapid Response Reports. Vitamin D for the Treatment or Prevention of Multiple Sclerosis: A Review of the Clinical Effectiveness.
- [46] Broła W, Sobolewski P, Szczuchniak W, Góral A, Fudala M, Przybylski W, Opara J. Association of seasonal serum 25-hydroxyvitamin D levels with disability and relapses in relapsing-remitting multiple sclerosis. *Eur J Clin Nutr* 2016; 70(9): 995-9.  
<https://doi.org/10.1038/ejcn.2016.51>
- [47] Muscogiuri G, Mitri J2, Mathieu C, Badenhop K, Tamer G, Orio F, Mezza T, Vieth R, Colao A, Pittas A. Mechanisms in endocrinology: vitamin D as a potential contributor in endocrine health and disease. *Eur J Endocrinol* 2014; 171(3): R101-10.
- [48] Kamen DL. Vitamin D in lupus - new kid on the block? *Bull NYU Hosp Jt Dis* 2010; 68(3): 218-22.
- [49] Antico A, Tampoia M, Tozzoli R, Bizzaro N. Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature. *Autoimmun Rev* 2012; 12(2): 127-36.  
<https://doi.org/10.1016/j.autrev.2012.07.007>
- [50] Abou-Raya A, Abou-Raya S, Helmii M. The effect of vitamin D supplementation on inflammatory and hemostatic markers and disease activity in patients with systemic lupus erythematosus: a randomized placebo-controlled trial. *J Rheumatol* 2013; 40(3): 265-72.  
<https://doi.org/10.3899/rheum.111594>
- [51] Bright JJ. Curcumin and autoimmune disease. *Adv Exp Med Biol* 2007; 595: 425-51.  
[https://doi.org/10.1007/978-0-387-46401-5\\_19](https://doi.org/10.1007/978-0-387-46401-5_19)
- [52] Laura J. McCreight, Clifford J. Bailey, and Ewan R. Pearson. Metformin and the gastrointestinal tract. *Diabetologia* 2016; 59: 426-435.  
<https://doi.org/10.1007/s00125-015-3844-9>
- [53] Peat CM, Kleiman SC, Bulik CM, Carroll IM. The intestinal microbiome in bariatric surgery patients. *Eur Eat Disord Rev* 2015; 23(6): 496-503.  
<https://doi.org/10.1002/erv.2400>
- [54] De Groot PF, Frissen MN, De Clercq NC, Nieuwdorp M. Fecal microbiota transplantation in metabolic syndrome: History, present and future. *Gut Microbes* 2017; 8(3): 253-267.  
<https://doi.org/10.1080/19490976.2017.1293224>

[55] Kootte RS, Levin E, Salojärvi J, Smits LP, Hartstra AV, Udayappan SD, Hermes G, Bouter KE, Koopen AM, Holst JJ, Knop FK, Blaak EE, Zhao J, Smidt H, Harms AC, Hankemeijer T, Bergman JJGGM, Romijn HA, Schaap FG, Olde Damink SWM, Ackermans MT, Dallinga-Thie GM, Zoetendal E, de Vos WM, Serlie MJ, Stroes ESG, Groen AK,

Nieuwdorp M. Improvement of insulin sensitivity after lean donor feces in metabolic syndrome is driven by baseline intestinal microbiota composition. *Cell Metab* 2017; 26(4): 611-619.

<https://doi.org/10.1016/j.cmet.2017.09.008>

Received on 20-08-2018

Accepted on 25-09-2018

Published on 14-12-2018

DOI: <https://doi.org/10.12970/2310-9874.2018.06.03>

© 2018 Alan Sacerdote; Licensee Synergy Publishers.

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.