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Adipose tissue expandability and the early origins of PCOS

Francis de Zegher[1], Abel Lopez-Bermejo[2] and Lourdes Ibáñez[3]

[1] Department of Woman & Child, University of Leuven, Belgium
[2] Pediatric Endocrinology, University of Girona, Spain
[3] Pediatric and Adolescent Endocrinology, Hospital Sant Joan de Deu, University of Barcelona, Spain

The most prevalent phenotypes of polycystic ovary syndrome (PCOS) are characterized by insulin resistance and androgen excess. The adipose tissue (AT) expandability hypothesis explains the development of insulin resistance in obesity and in cases of AT deficit. In line with this hypothesis, we propose that hyperinsulinemic androgen excess in PCOS is often underpinned by exhaustion of the capacity to expand subcutaneous AT in a metabolically safe way. Such exhaustion might occur when a positive energy imbalance meets a normal fat-storage capacity and/or when a normal energy balance faces a low fat storage capacity. This concept thus explains how PCOS phenotypes might result from obesity, prenatal growth restraint or a genetic lipodystrophy, or, experimentally, from prenatal androgen excess.

Polycystic ovary syndrome

The definition of polycystic ovary syndrome (PCOS) (Box 1) continues to be a matter of debate [1,2], but it has been known for decades that the most prevalent phenotypes of PCOS – both in obese and non-obese women – are hallmarked by a combination of insulin resistance and androgen excess [3,6]. Insulin resistance is a key factor in the pathogenesis of these PCOS phenotypes, as hyperinsulinemia increases ovarian androgen production and decreases hepatic sex hormone-binding globulin (SHBG) release, thereby leading to augmented levels of freely circulating androgens [3–9]. We propose a unifying concept on the developmental origins of hyperinsulinemic androgen excess and thus of the most prevalent – but not all – phenotypes of PCOS.

The ''adipose tissue expandability'' hypothesis

The "adipose tissue expandability" hypothesis, recently proposed by Virtue and Vidal-Puig, explains the development of insulin resistance in obesity and also the apparent paradox that insulin resistance might occur when there is a deficit of adipose tissue (AT) [10,11]. This hypothesis proposes that subcutaneous AT has a limited capacity to increase its mass safely. This capacity is individually determined by a wide range of environmental and genetic factors. When subcutaneous adipocytes start to be overfilled, a lipotoxic state emerges. Lipotoxicity is characterized by elevated free fatty acids, hypertriglyceridemia, an unfavorable adipocytokine profile [including low circulating levels of high molecular weight (HMW) adiponectin and high levels of interleukin-6 and tumor necrosis factor (TNF)-α] and by lipid deposition in non-subcutaneous AT and in non-adipose organs such as liver, muscle or pancreas. Lipotoxicity has adverse effects on metabolism, most notably on insulin action. According to this concept, metabolic health is maintained as long as the adipose depot can accommodate the caloric supply safely, that is, without causing lipotoxicity. The concept thus implies that there is a "metabolic setpoint", beyond which further lipid storage is rapidly accompanied by insulin resistance and its correlates (Figure 1) [10]. In this report, we propose that hyperinsulinemic androgen excess is commonly driven by exhaustion of the capacity to expand subcutaneous AT in a metabolically safe way (Figure 2).

Early growth and later expandability of subcutaneous AT

Among mammals, the human infant has by far the highest amount of subcutaneous AT for body weight; even baby seals have a lower level of subcutaneous adiposity [12]. In the human species, the adult number of subcutaneous adipocytes is essentially set in early life (age <2 years) and around puberty (age 10–18 years) [13,14]. Early life is the more dynamic of these two phases, characterized by a unique ensemble of rapid lipid deposition (about 0.5 g/hour), high insulin sensitivity and elevated HMW adiponectinemia [15,16]. In the fetus and breastfed infant, more than 90% of AT expansion occurs subcutaneously [17,18]. During prenatal growth restraint, the fetal expansion of AT is reduced, particularly in girls [14], raising the possibility that fewer pre-adipocyte precursors or smaller adipocytes are available for AT development [19]. If exposed to prenatal growth restraint, most human newborns will develop spontaneous catch-up growth, during which the swift recovery of fat-free mass is prioritized and the relative paucity of subcutaneous AT is further aggravated [16]. Hence, the sequence of fetal restraint and postnatal catch-up is accompanied by a marked reduction of subcutaneous AT in early infancy. Such a reduction within a crucial window of AT development might confer long-term risk for insulin resistance when caloric supplies become abundant. Girls of low birth weight with spontaneous catch-up growth are known to become relatively insulin-resistant, hypoadiponectinemic and viscerally adipose by 4–6 years of age [20–23]. However, in the absence of

Corresponding author: de Zegher, F. (Francis.deZegher@uzleuven.be).

1043-2760/$ – see front matter doi:10.1016/j.tem.2009.06.003 Available online 30 September 2009

Box 1. PCOS: definitions and prevalence

PCOS is an evolving concept. An early definition (National Institute for Child Health and Human Development, 1990) required that both clinical/endocrine hyperandrogenism and oligo-ovulation be present, and that specific etiologies (such as hyperprolactinemia and 21-hydroxylase deficiency) be excluded. This diagnosis of PCOS was thus independent of ovarian morphology [1]. The latest definition (Androgen Excess and PCOS Society, 2009) requires the presence of clinical/endocrine androgen excess, plus either chronic oligoovulation and/or polycystic morphology of the ovaries. The same exclusions still apply [2]. According to the latter definition, the prevalence of PCOS is estimated to be about 5–10% of premenopausal women, with a higher prevalence in obese than in non-obese women.

spontaneous catch-up growth, they remain insulin-sensitive and normoadiponectinemic, with a thin layer of abdominal subcutaneous AT and a normal amount of visceral AT [24]. Available evidence thus indicates that the sequence of fetal restraint and infantile catch-up reduces the capacity of AT to store fat safely in subcutaneous depots, and thereby lowers the adiposity threshold at which insulin resistance and other markers of lipotoxicity emerge.

Hyperinsulinemic androgen excess with a normal fat storage capacity

Obesity ensuing from a chronically positive imbalance between energy intake and output can exhaust a normal capacity to store fat safely, and lead to metabolic complications including insulin resistance and androgen excess and thus PCOS. This is the proposed explanation for the robust links between (primary) obesity, (secondary) hyperinsulinemia and (tertiary) hyperandrogenemia – links already established in prepuberty and persisting through puberty into adulthood [8,25,26]. An obesogenic lifestyle seems to be the main factor underpinning common variants of obesity; however, the role of genetic predisposition in various conditions, including PCOS, is increasingly recognized [27,28].

The AT expandability hypothesis also offers a rationale for how obese women might be protected from developing androgen excess, that is, they seem to have an enlarged capacity to store fat subcutaneously. For example, an ethnically Caucasian background tends to confer more subcutaneous capacity for fat storage than an African, native American, Middle or Far Eastern, aboriginal Australasian or South Asian origin [29,30]. Indian, Chinese and Japanese women, for example, are more prone than Caucasian women to develop hyperinsulinemic androgen excess and polycystic ovaries in response to overweight [31–33]. An accelerated expansion of AT in fetal and in early infant life confers additional protection against obesity-associated insulin resistance [34], perhaps by augmenting the recruitment of subcutaneous adipocytes or their individual capacity to store fat safely [18] (Figure 3).

From a therapeutic perspective, lifestyle measures are pivotal to reverse these phenotypes of hyperinsulinemic androgen excess [35], and their efficacy can be augmented by treatment with an insulin sensitizer such as metformin and with an androgen-receptor blocker such as flutamide [36–39]. This concept suggests that weight loss should be tailored individually, the aim being a reduction until weight falls within a woman's maximal fuel storage capacity. To gauge the latter, markers as fasting glucose, insulin, lipid profile, C-reactive protein, neutrophil count and HMW adiponectin might be useful, but remain to be validated in adolescents and women with PCOS [10].

Hyperinsulinemic androgen excess with a low fat storage capacity

The subcutaneous adipocytes of non-obese women with PCOS are enlarged by about 25% [40]. When the capacity to store fat is reduced, a normal caloric intake might act as

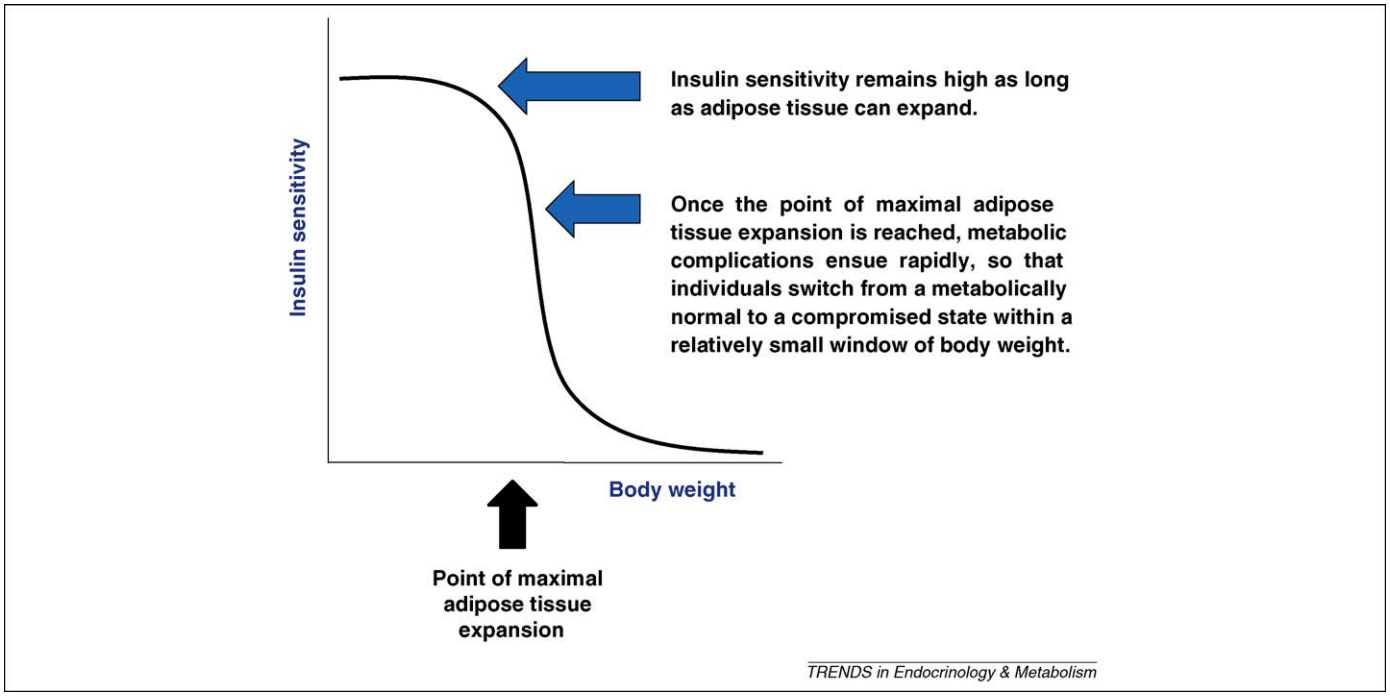

Figure 1. The concept of the metabolic setpoint [10].

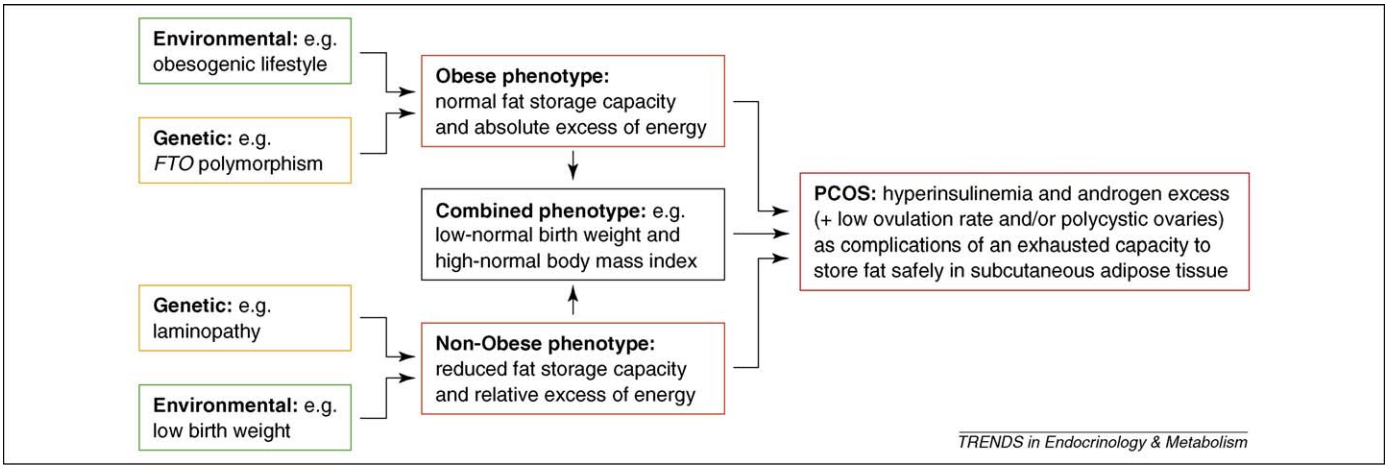

Figure 2. Summary of the ''adipose tissue expandability'' hypothesis on the early origins of PCOS, in particular, of the PCOS subgroup with hyperinsulinemic androgen excess. *FTO*: fat mass- and obesity-associated gene.

a relatively excessive supply and might be sufficient to exhaust such low capacity, leading to hyperinsulinemic androgen excess. This is the proposed explanation for the link between lipodystrophies and PCOS, and also between low birth weight and PCOS. Indeed, the majority of women with lipodystrophy due to a laminopathy develop hyperinsulinemic androgen excess, often with polycystic ovaries [41]. The birth weight of non-obese PCOS women tends to be low, particularly in women with either severe hyperinsulinemia [42,43], glucose intolerance [44] or non-polycystic ovaries [45].

There is emerging evidence that such phenotypes of hyperinsulinemic androgen excess can be reversed, without lowering body weight, by pharmacological expansion of subcutaneous AT with pioglitazone, a drug that can be added to a baseline therapy with metformin and flutamide. This combination treatment, even at low doses, seems not only to improve the adipocytokine profile (higher HMW adiponectin and visfatin; lower C-reactive protein) but also to attenuate dyslipidemia (lower triglycerides; lower ratio of low-density to high-density lipoprotein cholesterol), to reduce hyperinsulinemic androgen excess and to normalize intima media thickness [46–48].

Hyperinsulinemic androgen excess in daily practice

In the paragraphs above, we described models in which obese women with hyperinsulinemic androgen excess have an average birth weight and a body mass index (BMI) above normal, whereas non-obese women with hyperinsulinemic androgen excess have a birth weight below normal and an average BMI. In daily practice, non-obese patients with hyperinsulinemic androgen excess often have a low–normal birth weight and a high–normal BMI, and thus combine both models [38,39]. Ethnic variation should also

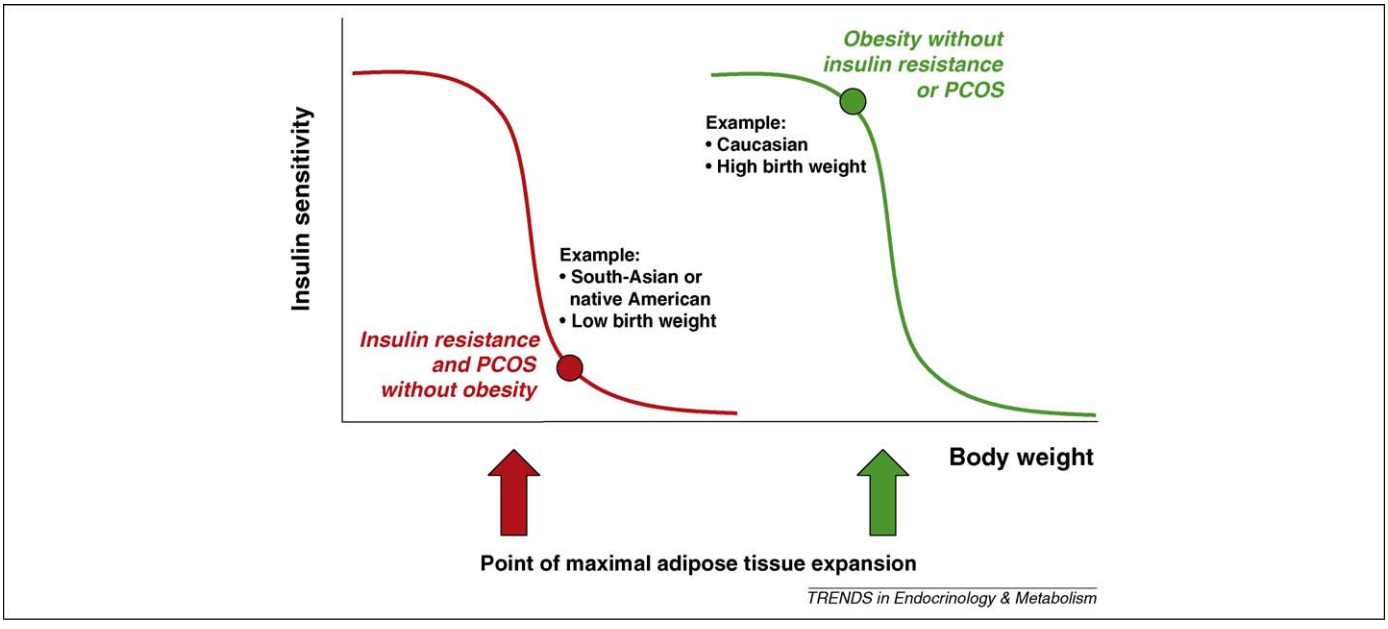

Figure 3. The individual setpoint, up to which adipose tissue can be safely expanded, depends on a broad variety of genetic and epigenetic factors. Some ethnic backgrounds, particularly when combined with growth restraint in early life, confer a setpoint of maximal adipose tissue expansion that is already reached at a relatively low body weight (red arrow), and thus may lead to a state of insulin resistance and PCOS without frank obesity. Other ethnic backgrounds, particularly when combined with favorable growth conditions in early life, confer a setpoint that is located at a higher body weight, possibly even beyond the threshold for obesity (green arrow), and may thus lead to a state of obesity without frank insulin resistance or PCOS.

be taken into account; in India, Pakistan and Bangladesh, for example, about a quarter of all girls have a birth weight below 2.5 kg [49]. Hyperinsulinemic androgen excess is influenced by a broad range of environmental and genetic factors, including polymorphisms that confer high androgen availability or sensitivity [26,50–52]; these all might contribute to accelerating gonadotropin-releasing hormone pulsatility and eliciting luteinising hormone hypersecretion [53] and thus to the development of a broad PCOS phenotype.

Prenatal androgen excess models of PCOS

Studies in sheep and non-human primates have established that prenatal testosterone administration to a female conceptus is followed not only by pseudohermaphroditism and masculinized behavior, but also by prenatal growth restraint (in sheep) and by insulin resistance and a PCOS-like phenotype into adulthood [54,55]. It is still uncertain how relevant these animal models are for the origins of the most common variants of human PCOS, because the particularly abundant aromatase activity of the human placenta normally protects unborn girls from exposure to maternal androgens [56] and because most women with PCOS do not have ambiguous genitalia. In addition, maternal androgenemia (through pregnancy) and fetal androgenemia (at birth) were found not to be elevated in girls who subsequently developed PCOS [57]. Conversely, the prevalence of PCOS was not elevated in women with a twin brother, who were thus born after an opposite-gender twin gestation, which implies a risk for prenatal androgen excess in the female conceptus [58].

Newborn boys are less adipose than girls [15], presumably in part because boys have higher androgenemia before birth, and because testosterone and dihydrotestosterone are potent inhibitors of adipogenic differentiation of preadipocytes into adipocytes [59]. Hence, inhibition of prenatal adipogenesis might be an underscored feature of androgen excess models in primates, sheep and rats [53,54,60]. The adiposity of fetal girls is normally about 5-fold higher than the adiposity of fetal primates or lambs, and about 10-fold higher than the adiposity of fetal rats [11]. The fetuses of these animals could thus be viewed as relatively "lipodystrophic" compared with fetal girls, and it is therefore not surprising that a further androgen-induced reduction of their already limited AT expansion might be followed by an adult phenotype mimicking that of metabolic syndrome [53,54,59]. The most pronounced PCOS phenotypes are observed in prenatally androgenized primates who developed a high BMI in adulthood [53], and in prenatally androgenized sheep who progress through the entire sequence from a low birth weight to a high BMI in adulthood [61]. The observations in models of prenatal androgen excess thus seem compatible with the unifying hypothesis that hyperinsulinemic androgen excess is commonly driven by exhaustion of the capacity to expand subcutaneous AT in a metabolically safe way.

Conclusion

The AT expandability hypothesis offers a rationale for the apparent paradox that both an excess and a deficit of AT might be associated with insulin resistance. A simple extension of this hypothesis allows the pathogenesis of major PCOS variants to be brought together under the same umbrella, namely under the exhaustion of the safe storage of fat. In addition, our unifying hypothesis harbors the seemingly conflicting evidence that experimental models of prenatal androgen excess can induce PCOS in some mammals, but that human PCOS is not commonly preceded by maternal/fetal androgen excess. Therefore, our hypothesis on the early origins of hyperinsulinemic androgen excess might warrant further investigation (Box 2).

Henceforth, adolescent PCOS could be viewed as the end-stage of a pediatric sequence, rather than as the beginning of a gynecological cluster. Indeed, cross-sectional studies determined that many obese girls already present hyperinsulinemic androgen excess before puberty or in early puberty [25,52], and longitudinal studies disclosed that girls of lower birth weights tend to become hyperinsulinemic, hypoadiponectinemic and viscerally adipose by 4–6 years of age [20–23].

One of the next challenges of incorporating the AT expandability hypothesis into a PCOS context will be to compare the effects of the currently standard treatment with an ovary-silencing estro–progestagen to those of a therapy that attenuates lipotoxicity and thereby reduces both hyperinsulinemia and androgen excess in young adolescents with hyperinsulinemic androgen excess.

Box 2. Outstanding Questions

The proposed hypothesis needs to be substantiated by more evidence. Adipocyte hypertrophy could be used as a marker for pre-adipocyte recruitment failure, thus pointing indirectly to a failure of (further) expandability. The following might be among the clinical research priorities:

- More evidence of adipocyte hypertrophy and/or lipotoxicity
  - in prepubertal girls with low birth weight and/or high BMI;
  - in non-obese and obese women with hyperinsulinemic androgen excess.
- Absence of adipocyte hypertrophy in obese women without PCOS.
- Confirmation of normal birth weight in non-biased cohorts of obese women with PCOS and confirmation of relatively low birth weight in non-biased cohorts of non-obese women with PCOS.
- Studies on the potential role of lipotoxicity in ovarian dysfunction and gonadotropin hypersecretion.

Acknowledgements

We thank Antonio Vidal-Puig and Samuel Virtue (University of Cambridge, UK) and Renato Pasquali (University of Bologna, Italy) for expert review of the manuscript. LI is supported by CIBERDEM, Instituto de Salud Carlos III, Madrid, Spain.

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