BODY COMPOSITION OF INDIVIDUALS WITH POLYCYSTIC OVARY SYNDROME

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[Composizione corporea in soggetti con sindrome dell'ovaio policistico]

SUMMARY

Polycystic ovary syndrome (PCOS) is one of the principle forms of hyperandrogenism that affects women of reproductive age. Few studies have evaluated the body composition of patients with PCOS being based mainly on an evaluation of the quantity and distribution of the fat mass.

Objectives: to evaluate the body composition of patients affected by PCOS and to establish the hormonal factors that determine possible differences in body composition compared with healthy women.

Methods: 110 Caucasian women affected by clinical hyperandrogenism and/or irregular menstrual periods were included in the study; the control group was made up of 90 healthy Caucasian women, of reproductive age, without hyperandrogenism. The control group and the patients were similar in age (23 ± 3 vs. 24.1 ± 6.4 years old) but not in body weight or body mass index (BMI). A hematic sample was taken from both groups, on the fifth day of the menstrual cycle, to measure the quantities of glycaemia, insulin, testosterone (T), SHBG and dehydroepiandrosterone sulphate (DHEAS). In the hyperandrogenic patients the quantities of serum 17-hydroxyprogesterone (on the 5th day of the menstrual cycle) and of progesterone (on the 22nd day of the menstrual cycle) were also measured. Moreover, the hyperandrogenic patients underwent a pelvic or intra-vaginal ultrasound scan to evaluate the ovarian morphology.

Results: the patients with classic PCOS showed serum levels higher in testosterone, FAI and insulin than the patients with ovulatory PCOS and idiopathic hyperandrogenism; the patients with ovulatory PCOS had higher levels of testosterone, FAI and insulin ($p<0.01$) than the control group. The patients with Idiopathic Hyperandro-genism had higher levels of testosterone ($p<0.01$) and FAI ($p<0.01$) but similar levels of BMI and insulin, and similar waist circumference and body composition.

Conclusions: the hyperandrogenic patients have a different body composition to normal women. The increase in the fat free mass seems to be primarily a consequence of hyperinsulinemia, as the fat free mass correlated significantly with the circulating insulin and the insulin resistance. Consequently, these alterations have an influence on the body composition and therefore both on the quantity and distribution of body fat and on the increase in muscle mass.

Key words: Polycystic ovary syndrome, body composition, hyperinsulinemia

RIASSUNTO

La sindrome dell'ovaio policistico (PCOS) è una delle principali forme di iperandrogenismo che colpisce le donne in età fertile. Pochi studi hanno valutato la composizione corporea nelle pazienti con PCOS basandosi prevalentemente su una valutazione della quantità e distribuzione della massa grassa.

Obiettivi: *valutare la composizione corporea nelle pazienti affette da PCOS e stabilire quali sono i fattori ormonali che determinano le eventuali differenze in composizione corporea rispetto alle donne sane.*

Metodi: *Sono state incluse nello studio 110 donne di origine caucasica affette da iperandrogenismo clinico e/o irregolarità mestruali; il gruppo di controllo è stato costituito da 90 donne caucasiche sane, in età fertile, senza iperandrogenismo. Controlli e pazienti erano paragonabili per età (23.6 ± 3 vs 24.1 ± 6.4 anni) ma non per peso corporeo e indice di massa corporea (BMI). In entrambi i gruppi è stato effettuato prelievo ematico, al 5° giorno del ciclo mestruale, per il dosaggio di glicemia, insulina, testosterone (T), SHBG e deidroepiandrosterone solfato (DHEAS). Nelle pazienti iperandrogeniche è stato effettuato anche il dosaggio di 17-idrossiprogesterone sierico (al 5° giorno del ciclo mestruale) e di progesterone (al 22° giorno del ciclo mestruale). Inoltre le pazienti iperandrogeniche sono state sottoposte a ecografia pelvica o intravaginale per la valutazione della morfologia ovarica.*

Risultati: *le pazienti con PCOS classica presentavano livelli sierici più elevati di testosterone, FAI e insulina rispetto alle pazienti con PCOS ovulatoria e iperandrogenismo idiopatico; le pazienti con PCOS ovulatoria avevano rispetto ai controlli aumentati valori di testosterone, FAI e insulina ($p<0.01$). Le pazienti con Iperandrogenismo Idiopatico avevano rispetto ai controlli livelli più elevati di testosterone ($p<0.01$) e FAI ($p<0.01$) ma valori similari di BMI, insulina, circonferenza vita e composizione corporea.*

Conclusioni: *le pazienti iperandrogeniche presentano una diversa composizione corporea rispetto alle donne normali. L'aumento della massa magra sembra essere in primo luogo la conseguenza dell'iperinsulinemia poichè la massa magra correlava significativamente con l'insulina circolante e con la resistenza insulinica. Queste alterazioni pertanto hanno delle influenze sulla composizione corporea e quindi sia sulla quantità e distribuzione del grasso corporeo sia sull'aumento della massa muscolare.*

***Parole chiave**: Sindrome dell'ovaio policistico, composizione corporea, iperinsulinemia*

Introduction

The human body is made up of numerous elements, but body composition is conventionally expressed with two principal categories: Fat Mass (FM) and Fat Free Mass (FFM).

The Fat Mass is the weight of only the fat in the organism (subcutaneous and perivisceral), and the Fat Free Mass is the weight of all the other organic components including the muscular and skeletal mass and the bone mineral component, but above all water, which constitutes about 73% of the total FFM.

The muscular and skeletal mass, for example, represents about 40% of the body weight of a young adult and in general this decreases with age, with a loss of about 30% of its value at a more advanced age[1]. Reference percentages have also been created for the Fat Mass of people aged between 20 to 80, taking into consideration differences related to sex and ethnicity as well as age[2,3].

These variations are influenced by genetic, diet and nutritional, behavioural, socio-economic, environmental and hormonal factors, including sex hormones, glucocorticoids, GH and IGF-1[4,5,6].

Sex hormones, GH, insulin, glucocorticoids and androgenic β-3 agonists are important determiners of the adipocerous mass. Acting on the target cells, testosterone, GH and androgenic β-3 agonists bring on lipolysis of both the visceral and the subcutaneous adipose tissue. Insulin, cortisol and estrogen, on the other hand, stimulate lipogenesis.

In fact, the adipose tissue is both an energy depositing tissue and an endocrine organ, and it is intensely active from the metabolic point of view[7,8]: it has many receptors that allow it to respond both to hormonal afferent signals and to afferent signals that come from the central nervous system; it synthesizes and secretes a wide variety of active peptides, known as adipochins, including leptin and adiponectin, TNFα (Tumour necrosis factor α), Interleukin 6 (IL-6) and plasminogenic activator inhibiter (PAI-1), which are able to act both at a local level (autocrine and paracrine action) and at a systemic level (endocrine action).

Quantifying body composition

Body composition can be evaluated using various different methods that vary in their complexity and precision: they range from the most simple, like anthropometric testing, plicometry and bioelectrical impedance analysis (BIA), to more technically complex ones, like DEXA (Dual Energy X-ray Absorptiometry), plethysmography, CT (Computerised Tomography) and MRI (Magnetic Resonance Imaging)[9]. The calculation of the BMI (Body Mass Index) is simpler. With a simple formula it puts in relation two easily obtainable anthropometric parameters, that is, height and weight [BMI: weight in Kg/ height in m^2], allowing a differentiation to be made between the individuals who are underweight [BMI < 18.5 Kg/m^2], of normal weight [BMI 18.5-24.9 Kg/ m^2], overweight [BMI 25.0-29.9 Kg/m^2] and obese [BMI >30.0 Kg/m^2], as well as the grade of obesity [grade I: BMI 30.0-34.9 Kg/ m_; grade II: BMI 35.0-39.9 Kg/m^2; grade III: BMI ≥ 40.0Kg/m^2][10].

It is a very useful indicator, but it has some important limitations connected, above all, to the fact that it cannot quantify body composition, and therefore tell whether the excess in weight is due to an increase in fat mass or fat free mass.

However, BMI becomes a good predictor of the total and visceral fat mass if it is associated with other anthropometric parameters: the circumference of the waist and the waist-hip ratio. According to European guidelines the circumference of the waist should not exceed 102 cm for men and 88 cm for women. The waist/hip ratio should be less than 0.95 for men and 0.8 for women.

The circumference of the waist is closely correlated to visceral fat[11], and was included as one of the risk factors and diagnostic criteria for metabolic syndrome in the document Adult Treatment Panel III (ATP III) by the National Cholesterol Education Program[12].

Furthermore, a meta-regression analysis of perspective studies published in 2007 in the European Heart Journal, showed that the incidence of cardiovascular events rose with the increase in the circumference of the waist and the WHR: in particular, an increase in waist circumference of 1cm was associated with an increase in the relative risk (RR) of the incidence of cardiovascular events, and an increase of 0.01 in the waist-hip ratio was associated with a 5% increase in the RR of the incidence of cardiovascular events[13]. A more complex method of evaluating body composition can be obtained by using DEXA (dual energy x-ray absorptiometry). It is a tri-compartmental evaluation model, and since it is based on the differences that exist between the various tissues connected with two peaks in x-ray energy, it can provide both total and regional quantitative evaluations of Fat Mass (FM), Lean Mass (LM), and Bone Mass.

It is able to determine the Bone Mineral Content in grams (BMC) of the Bone Mass as well as the Bone Mineral Density in g/cm^2 (BMD)[4].

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is one of the main hyperandrogenic syndromes that affect 5-10% of women of reproductive age, or better, approximately 1 in every 15 women of reproductive age, for a total of 450 million women around the world[14,15,16].

In 2003, during a meeting between the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), new guide lines emerged according to which the diagnosis of PCOS requires the presence of at least 2 of the following criteria: 1) clinical or biochemical hyperandrogenism; 2) chronic oligo-anovulation; 3) ultra sound scan evidence of polycystic ovaries; as well as the exclusion of other causes of hyperandrogenism such as congenital adrenal hyperplasia, androgen secreting tumours, cushing's syndrome, etc.[17] (table 1).

The new diagnostic criteria have had important consequences for the classification of hyperandrogenic syndromes, leading to the distinction of 3 main phenotypes of hyperandrogenism[18]:

1) ***Classic PCOS***: hyperandrogenism + chronic anovulation ±polycystic ovaries;

2) ***Ovulation PCOS***: hyperandrogenism + polycystic ovaries + ovulation cycles;

3) ***Idiopathic hydroandrogenism***: hyperandrogenism + ovulation cycles and morphologically normal ovaries.

Starting from common pathogenic substrates, the clinical expression of one or other phenotype results from the presence of different genetic and environmental factors, of which one of the principal ones, as demonstrated by various different studies, seems to be body weight and more precisely obesity[18].

Objectives of the study

Only a few studies have evaluated body composition in patients with PCOS.

These studies are generally limited to an evaluation of the quantity and distribution of fat mass [19,20,21].

Definition / year(Ref.)	Diagnostic criteria	Possible phenotypes	Exclusion criteria	Clinical hyperandrogenism	Biochemical hyperandrogenism	PCOM (PCOS)
NICHD / 1990 (10)	Requires simultaneous presence of: *1)* Clinical and/or biochemical hyperandrogenism *2)* Menstrual dysfunction	*1)* Clinical and/or biochemical hyperandrogenism + Menstrual dysfunction	Congenital adrenal hyperplasia, androgen secreting tumours, cushing's syndrome, hyperprolactinemia	Hirsutism, alopecia and acne	*1)* Total testosterone, *2)* Free testosterone *3)* Androstenedione *4)* DHEAS	Not included
Rotterdam / 2003 (11)	Requires the presence of at least 2 of the following 3 criteria: *1)* Clinical and/or biochemical hyperandrogenism *2)* Ovulatory dysfunction *3)* PCOM	*1)* Clinical and/or biochemical hyperandrogenism + ovulatory dysfunction *2)* Clinical and/or biochemical hyperandrogenism + Ovulatory dysfunction + PCOM *3)* Clinical and/or biochemical hyperandrogenism + PCOM *4)* Ovulatory dysfunction + PCOM	Congenital adrenal hyperplasia, androgen secreting tumours, cushing's syndrome	Hirsutism, androgenic acne and alopecia?	*1)* Free androgen index (FAI) or free testosterone *2)* Total testosterone and *3)* DHEAS	Al least one ovary with evidence of: *1)* 12 or more follicles (2-9 mm in diameter) *2)* Ovary volume > 10 ml
AES / 2006 (12)	Requires the presence of clinical and/or biochemical hyperandrogenism + *1)* oligo-anovulation and/or *2)* PCOM	*1)* clinical and/or biochemical hyperandrogenism + oligo-anovulation *2)* clinical and/or biochemical hyperandrogenism + oligo-anovulation + PCOM *3)* clinical and/or biochemical hyperandrogenism + PCOM	Congenital adrenal hyperplasia, androgen secreting tumours, use and abuse of androgenic/anabolic drugs, Cushing's syndrome, severe insulin-resistance syndrome. Thyroid dysfunction. hyperprolactinemia	Hirsutism	*1)* Free androgen index (FAI) or free testosterone *2)* Total testosterone *3)* DHEAS and *4)* androstenedione	Al least one ovary with evidence of: *1)* 12 or more follicles (2-9 mm in diameter) *2)* Ovary volume > 10 ml

Table 1: PCOS diagnostic criteria.

Some studies have also taken into consideration bone mass in patients affected with PCOS, but the data is contradictory[24,25,26].

There is no data available on the body composition of polycystic patients with regard to muscle mass, and whether differences exist between the different types of phenotypes of hyperandrogenism has not been evaluated either. The objectives of our study are:

1) Evaluating body composition in patients affected with PCOS so as to determine total fatty mass and the presence of abdominal obesity, and also bone and muscle mass.

2) Establishing which hormonal factors determine possible differences in body composition between polycystic women and healthy women.

3) Verifying the existence of differences in body composition in the various phenotypes of hyperandrogenism as these can be differentiated from each other from a hormonal point of view, not so much because of the levels of androgens as for the levels of insulin.

Methods and materials

Our study included 110 Caucasian women, who had been referred to the departments of Endocrinology and Internal Medicine of the medical field units of Internal Medicine and Metabolic diseases at the University Hospital "P.Giaccone" of Palermo, because of clinical hyperandrogenism and/or menstrual irregularity. The control group was made up of 90 healthy Caucasian women, of reproductive age, without clinical or biochemical hyperandrogenism and with regular menstrual cycles.

Those women with a clinical history that included diabetes, high blood pressure and liver and/or kidney failure were excluded from the study.

Moreover, none of the patients was taking and/or had taken oral contraceptives and/or drugs with a noticeable influence on hormonal, metabolic and bone parameters, in the six months previous to the study. The control group and the patients were of similar age (23.6 ± 3 vs. 24.1 ± 6.4 years old) but did not have similar body weights or Body Mass Indexes (BMI).

For the participants the study included a medical visit, a blood sample taken for biochemical analysis (on the 5th day of the menstrual cycle and also on the 22nd for the hyperandrogenic patients) and a DEXA examination to determine the bone density and body composition.

Patients and controls underwent a medical visit, and height, weight, BMI and circumference of the waist (measured at the level of the mid point between the lateral iliac crest and the margin of the last rib after a normal out-breath) were measured.

In the patients and in the healthy controls a blood sample was taken on an empty stomach between 8:00 and 10:00 a.m., on the 5th day of the menstrual cycle, for quantities of glycaemia, insulin, testosterone (T), SHBG and dehydroepiandrosterone sulphate (DHEAS).

In the hyperandrogenic patients samples of 17-OH-progesterone serum (on the 5th day of menstrual cycle) and of progesterone (on the 22nd day of menstrual cycle) were also taken.

Furthermore, hyperandrogenic patients underwent pelvic or intravaginal ultrasonography to evaluate ovary morphology.

Clinical hyperandrogenism was diagnosed on the basis of the presence of hirsutism, assessed using the Ferriman-Gallwey-Lorenzo Score[22].

Patients with a score >6 were considered affected by hirsutism.

Biochemical hyperandrogenism was diagnosed in the presence of levels of Testosterone serum > 60 ng/dl (>2.08 nmol/L) and/or DHEAS serum ≥3000 µg/L (≥7.8 µmol/L).

These results were previously calculated in our population using the same methods[23].

Anovulation was defined by a progesterone serum value < 3 ng/ml (< 9.54 nmol/L).

In patients with regular menstrual cycles, the diagnosis of chronic anovulation was made in the presence of progesterone levels < 3 ng/ml in at least two consecutive menstrual cycles.

The diagnosis of polycystic ovaries was determined through ultrasonography in the presence of at least 12 micro-cysts (2-9mm in diameter) in at least one ovary and/or in the presence of an ovary volume > 7.5 cc^3.

The diagnosis of classic PCOS was determined by the presence of clinical and/or biochemical hyperandrogenism and chronic anovulation, and the diagnosis of ovulation PCOS was determined in patients with clinical and/or biochemical hyperandrogenism, ovulation cycles and ultrasonography evidence of polycystic ovaries.

The diagnosis of Idiopathic hyperandrogenism was determined in patients with clinical and/or biochemical hyperandrogenism, ovulation cycles and normal ovary morphology in the ultra sound scan.

Results

The hyperandrogenic patients and the control group had similar height (162.2 cm vs 161.7, NS), but different BMI (23.8 ± 3.3 vs. 27.4 ± 5, p<0.01), girth (83.4 ± 6.3 vs. 92.4 ±10, p<0.01), fat free mass (256.3 ± 27 vs. 268.3 ± 35, p< 0.01), total fat mass (g 18982 ± 6017 vs. 25822 ± 8035, p< 0.010), trunk fat mass (g 6954 ± 2953 vs. 10618 ± 4897, p<0.01), trunk fat mass % (35.7 ± 5 vs. 39.7 ± 5, p< 0.01) and different serum levels of testosterone (35.0 ± 13.0 vs. 71.8 ± 27.9, p< 0.01), DHEAS (p<0.01), FAI (2.0 ± 0.8 vs. 8.4 ± 4.6, p<0.01) and insulin (9.6 ± 3 vs. 13 ± 5 microUI/ml,p<0.01).

No remarkable differences were diagnosed between the patients and the control group with regard to BMD and Z-score. (Table 2).

	Hyperandrogenic patients N = 110	**Check-ups N = 92**
Age	24.1 ± 6.4	23.6 ± 3.0
Height (cm)	161.7 ± 0.06	162.2 ± 0.07
BMI	27.4 ± 5*	23.8 ± 3.3
Waist measurement	92.4 ± 10*	83.4 ± 6.3
Total lean mass (g)/h (cm)	268.3 ± 35*	256.3 ± 27
Total fat mass (g)	25822 ± 8035*	18982 ± 6017
Trunk fat (g)	10618 ± 4897*	6954 ± 2953
Trunk fat %	39.7 ± 5*	35.7 ± 5
Testosterone (ng/dl)	71.8 ± 27.9*	35.0 ± 13.0
FAI	8.4 ± 4.6*	2.0 ± 0.8
Insulina (μU/ml)	13 ± 5*	9.6 ± 3.0
Bone Mineral Density (BMD)	1.092 ± 0.06	1.110 ± 0.07

* = p<0.01

Table 2: anthropometric, biochemical and pertaining parameters to the body composition in hyperandrogenic patients and in check-ups.

Of the hyperandrogenic patients, 72 were affected by classic anovulation PCOS, 23 by ovulation PCOS and 15 by a hyperandrogenic syndrome different from PCOS (idiopathic hyperandrogenism).

As demonstrated in table 3, the three groups of patients had similar age and height but the patients with classic PCOS had higher testosterone serum levels, FAI and insulin in comparison to patients with ovulation PCOS and idiopathic hyperandrogenism.

	C-PCOS N = 72	OV-PCOS N = 23	HI N = 15	Check-ups N = 92
Age	24.5 ± 6.4	24.8 ± 5.3	23.2 ± 6.4	23.6 ± 3.0
Height (cm)	160.2 ± 0.07	162.9 ± 0.05	167.8 ± 0.05	162.2 ± 0.07
Testosterone (ng/dl)	76.1 ± 33.0 *	60.1 ± 18.5 **	69.0 ± 17.8 ***	35.0 ± 13.0
FAI	9.1 ± 4.9 *	7.5 ± 5.6 **	6.6 ± 1.8***	2.0 ± 0.8
Insulina (μU/ml)	14.8 ± 6.1 *	11.3 ± 4.1 **	10.6 ± 3.9	9.6 ± 3.0
QUICKI	0.328 ± 0.02 *	0.338 ± 0.02 **	0.337 ± 0.02	0.348 ± 0.02

C-PCOS: classic PCOS
OV-PCOS: ovulation PCOS
HI: idiomatic hyperandrogenism
* C-PCOS vs check-ups: p<0.01; C-PCOS vs OV-PCOS e HI: p<0.05
** OV-PCOS vs check-ups: p< 0.01
*** HI vs check-ups: p<0.01.

Table 3: anthropometric and biochemical parameters in the three hyperandrogenic phenotypes and in check-ups.

Furthermore, as demonstrated in table 4, patients with classic PCOS, in comparison to other hyperandrogenous groups, had higher levels of BMI, girth, total fat free mass, total fat mass and trunk fat mass, both in total values and %.

	C-PCOS N = 72	OV-PCOS N = 23	HI N = 15	Check-ups N = 92
BMI	28.4 ± 5.7 *	25.2 ± 3.6	23.2 ± 3.0	23.8 ± 3.3
Waist measurement	194.7 ± 13.6 *	186.4 ± 10.5	84.7 ± 9.0	83.4 ± 6.9
Total lean mass (g)/h (cm)	274.9 ± 37.9 *	258.4 ± 35.6	249.4 ± 32.4	256.3 ± 26.9
Total fat mass (g)	26660 ± 9527 *	22835 ± 6007	21546 ± 4638	18982 ± 6083
Trunk fat (g)	11421 ± 5276 *	8482 ± 2850 **	7975 ± 2573	6954 ± 2986
Trunk fat %	41.3 ± 6 *	36.4 ± 5 **	36.4 ± 4	35.7 ± 5

C-PCOS: classic PCOS
OV-PCOS: ovulation PCOS
HI: idiomatic hyperandrogenism
* C-PCOS vs controlli: p<0.01; C-PCOS vs OV-PCOS e HI: p<0.05
** OV-PCOS vs controlli: p<0.02

Table 4: parameters pertaining to the body composition in the three hyperandrogenic phenotypes and in the control group**.**

Patients with ovulation PCOS, in comparison to the control groups, had higher levels of testosterone, FAI and insulin (p<0.01).

The study of body composition demonstrated that patients with ovulation PCOS had similar values of BMI (25.2 ± 3.3 VS 23.8 ± 3.3, NS), girth, fat free mass, total fat mass and bone mineral density (BMD), but higher values of trunk fat both in g ($p<0.02$) and in % ($p<0.02$), in comparison to the control groups.

Discussion

Our data indicates that hyperanrogenic patients have a different body composition to normal women. Nevertheless, these differences are mainly attributable to women with classic polycystic ovary syndrome. These patients show not only an increase in fat mass and an altered distribution of fat with a prevalence of abdominal fat, but also an increase in fat free mass and therefore in the muscular component.

On the other hand, neither the patients with the minor phenotype of ovulation PCOS, nor the patients with idiopathic hyperandrogenism show alterations in body composition, and they both have a normal quantity of fat free mass and fat mass and a normal distribution of body fat. The increase in the fat free mass in patients with classic PCOS is something that has not previously been discussed.

In the past, before the new criteria for diagnosing PCOS and the differentiation between the various phenotypes of hyperandrogenism, an increase in the fat free mass of hyperandrogenic patients was reported without distinguishing between the different forms. Moreover, the increase in the fat free mass was attributed to the increase in androgens.

Our data suggests that the increase in the fat free mass is primarily a consequence of hyperinsulinemia. In fact, although the patients with classic PCOS show higher levels of testosterone than those with ovulation PCOS and idiopathic hyperandrogenism, no correlation between fat free mass and circulating testosterone has been found. Moreover, although the patients with ovulation PCOS and idiopathic hyperandrogenism show significantly higher levels of testosterone than normal women (levels of about double), they do not show alterations in body mass or increases in fat mass.

However, the fat free mass correlated significantly with the circulating insulin and with the insulin resistance. A correlation was also found with the FAI, but it should be remembered that circulating insulin inhibits the synthesis of SHBG, contributing to the reduction in the serum concentration.

In conclusion, our data indicates that women with classic polycystic ovary syndrome show a complex modification in body composition, which involves not only the quantity and distribution of body fat, but also an increase in the muscle mass.

Further studies are necessary to determine how this factor may affect metabolic alterations in these patients.

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