

FEBRUARY NEWSLETTER

INFLUENCE OF ANDROGENS ON INFLAMMATION IN PCOS

February newsletter is dedicated to the possible influence of androgens on immune system and inflammation in women with PCOS. The editor has interviewed Frank Gonzalez, M.D., Associate Professor of Obstetrics and Gynecology and Director of the Division of Reproductive Endocrinology and Infertility at Indiana University School of Medicine, Indianapolis, IN, USA. Frank is member of AEPCOS Society from 2005 and has extensively studied the role of immune factors on development and clinical expression of PCOS.

Some important information about 12th Annual Meeting of AEPCOS Society are reported. The meeting will be held at Kauai Marriott Resort Hotel and Beach Club, Kalapaki Beach, Kauai, HI, USA, October 22-23, 2014.

Abstract deadline is September 7th, 2014. For abstract form, please connect to: www.ae-society.org or contact: info@ae-society.org

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In this issue:

- * Androgens and inflammation in PCOS
- * 12th Annual Meeting of AEPCOS Society

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FORTHCOMING AEPCOS MEETINGS

- 12th Annual Meeting of Androgen Excess & PCOS Society, Kauai Marriott Resort Hotel and Beach Club, Kauai, Hawaii, USA, October 22-23, 2014
- Update Meeting of AEPCOS Society, San Diego, CA, USA, March 4, 2015
- 13th Annual Meeting of AEPCOS Society, Palermo, Italy, October 4-6, 2015

12TH AEPCOS ANNUAL MEETING, KAUAI, HAWAII, OCTOBER 22-23, 2014

The 12th Annual meeting of the AEPCOS Society will be held at Kauai Marriott Resort Hotel and Beach Club, Kalapaki Beach, Kauai, Hawaii, USA, October 22-23, 2014, immediately after the Honolulu ASRM Annual Meeting. The venue of next annual meeting is a wonderful resort that is located in the very beautiful island of Kauai. The airport of Lihue, only one mile from the resort, may be reached by a



short 20 minutes flight from Honolulu. Several airlines serve this route with more than 10 daily flights. Lihue airport may be reached also by daily direct flights leaving from main Western USA and Canada cities including Los Angeles, San Francisco, Phoenix, Seattle and Vancouver. We have negotiated a very good rate at the Kauai Marriott that will be available to all registered guests for the duration of the meeting and for the following three days. Resort fee is optional but registration includes free shuttle bus from the airport. **As a special bonus for pre-registered (before October 1, 2014) AEPCOS and ASRM members flying to Lihue from Honolulu, we will reimburse \$100 of the ticket price (actual cost of the return ticket is \$103). AEPCOS members flying directly to Lihue from continental USA will get \$50 reimburse.**

The meeting program will include invited lectures, meet the professor sessions and oral communications

REGISTRATION FORM

12TH AEPCOS ANNUAL MEETING

REGISTRATION ONLY

_____ AEPCOS members \$260 _____ Non AEPCOS members \$360

KAUAI MARRIOTT RESORT HOTEL AND BEACH CLUB

\$219 for night

____ October 22 ____ October 23 _____ Number and dates of additional nights

Payment amount: \$ _____ Credit card payment: _____ VISA _____ MasterCard _____ AMEX

Credit card number _____ Expiration date: ____/____ CVV _____

Cardholder
name _____

Online payment _____ To safely pay online, connect to: www.ae-society.org

Check payment _____ Make checks payable to Androgen Excess Society

Email, mail or fax the registration form to: Androgen Excess & PCOS Society, via delle Croci 47, 1st floor, suite 10, 90139 Palermo, Italy. Fax: +39-091328997, Email: info@ae-society.org

Only written cancellation by fax or e-mail will be accepted. For cancellations until September 1, 2013, a 50% fee will be applied. No refund will be given after that date. Registration includes lunch, 2 coffee breaks and transportation from the airport. Price of the rooms are for garden view rooms. Add \$30 for partial ocean view. Hotel prices do not include 13.42% taxes that may be paid directly at the hotel. Resort fee (\$30 daily) is optional.

Pre-registered (before October 1, 2014) AEPCOS and ASRM members flying the route Honolulu-Lihue will get a reimburse of \$100 of air ticket price. Pre-registered AEPCOS members flying directly to Lihue from continental USA will get a reimburse of \$50. Reimburses will be available at the meeting. ASRM members should provide proof of their membership.

The certificate will be issued to the name of the accredited participant.

ABSTRACT SUBMISSION FOR 12TH AEPCOS ANNUAL MEETING

You are invited to submit abstracts of your original research to be considered for presentation at the 12th Annual Meeting of the Androgen Excess & Polycystic Ovary Syndrome Society. For abstract form, connect to: www.ae-society.org or contact: info@ae-society.org

To be considered for presentation your abstract must be submitted no later than September 7th, 2014, 11:00 pm (2300 hrs) PST. All abstracts must be submitted by email in word to: info@ae-society.org. The presenter is required to register for 12th Annual Meeting of the AE-PCOS Society on submission of the abstract

All abstracts will be reviewed by a blinded scientific committee nominated by AE-PCOS Annual Meeting Committee. Accepted abstracts will be published on the abstract book and presented as oral communications.

The Baumgartner-Azziz AE-PCOS fund will award 2 Travel Awards (\$750 each) to the best abstracts presented by young (<35 years) investigators.

OTHER MEETINGS

- **PATH meeting:** Estrogen exposure and metabolism. March 21-22, 2014, Bethesda Marriott, Bethesda, MD 20184, USA
- European Society of Endocrinology Annual Meeting, May 3-7, 2014, Wroclaw, Poland
- Endocrine Society Annual Meeting: June 21-24, 2014, Chicago, IL, USA
- ESHRE Annual Meeting, June 29-July 2, 2014, Munich, Germany
- ASRM Annual Meeting: October 20-22, 2014, Honolulu, HI, USA
- 12th Annual World Congress on Insulin Resistance Diabetes and Cardiovascular Disease. November 20-22, 2014, Sheraton Hotel Universal City, Los Angeles, CA, USA

ANDROGEN EXCESS & PCOS SOCIETY

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Frank Gonzalez, M.D.

INFLUENCE OF ANDROGENS ON INFLAMMATION IN PCOS

In this month's Newsletter, Enrico Carmina interviewed Dr. Frank González, who commented on his recent publication in Journal of Clinical Endocrinology and Metabolism 2014, February 10 [Epub ahead of print], entitled, "[HYPERANDROGENISM INDUCES A PROINFLAMMATORY TNF \$\alpha\$ RESPONSE TO GLUCOSE INGESTION IN A RECEPTOR-DEPENDENT FASHION.](#)" This study reports a possible mechanism by which hyperandrogenism may impact the immune system to generate a low grade inflammatory response.

1. Frank, What was the objective of your study?

Frank Gonzalez: In our previous studies, we showed that in PCOS, glucose ingestion triggers a prooxidant, proinflammatory response from circulating mononuclear cells (MNC) that is completely independent of excess adiposity. This response was highly correlated with circulating androgens raising the question whether hyperandrogenism is capable of activating MNC and sensitizing them to glucose as a potential underlying cause of the observed immune alteration in PCOS. In subsequent studies, we induced oxidative stress and low grade inflammation in an uninfamed cohort of lean healthy reproductive-age women by administering an oral androgen preparation to raise circulating androgens to levels observed in PCOS. At the molecular level, induction of hyperandrogenism upregulated the pathways responsible for oxidative stress and inflammation in the fasting state and in response to glucose ingestion. This confirmed that hyperandrogenism can activate MNC and increase MNC sensitivity to glucose. However, the mechanism for this phenomenon remained unclear. Based on the published literature, we hypothesized that the androgen receptor is involved in this mechanism.

The aim of the study was to determine the effect of hyperandrogenism on androgen receptor activity and TNF α release from cultured MNC as a measure of inflammation in the previously studied cohort of lean healthy reproductive-age women. The effect was evaluated in response to androgen administration *in vivo* that achieved androgen levels observed in PCOS and to androgen exposure at physiologic concentrations *in vitro*.

2. Can you summarize your findings?

Frank Gonzalez: The study revealed increases in androgen receptor mRNA content and TNF α release from MNC in the fasting state and following glucose ingestion in response to androgen administration *in vivo* and increases in TNF α release from MNC in response to androgen exposure *in vitro*. During the *in vitro* experiment, preincubation with flutamide which is a potent competitive inhibitor of the androgen receptor, reduced the TNF α response by $\geq 60\%$.

These data show that the inflammatory response from MNC of lean healthy reproductive-age women induced by hyperandrogenism is mediated through the androgen receptor. The androgen-stimulated proinflammatory TNF α response confirms our previous report that hyperandrogenism activates MNC and increases MNC sensitivity to glucose ingestion.

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3. What are the implications of your findings as it relates to PCOS?

Frank Gonzalez: It is well established that at the molecular level, low grade inflammation is involved in downregulating the insulin signaling pathway and upregulating proatherothrombotic pathways that culminate in insulin resistance and atherosclerosis. Indeed, we have previously shown that in PCOS, glucose-stimulated inflammation is inversely correlated with insulin sensitivity and can raise molecular markers of atherothrombosis. The new data from this paper extend our previous findings to suggest that hyperandrogenism may be the driver of these downstream metabolic abnormalities that promote insulin resistance, glucose intolerance and cardiovascular risk in PCOS.

The implications discussed should be viewed with caution because it is extrapolated from acute responses in women who do not have PCOS. Furthermore, inflammation was not reduced in lean women with PCOS when we chronically suppressed hyperandrogenism in PCOS. These findings are important because they show that once the chronic state is established, hyperandrogenism may not promote inflammation in PCOS. This suggests an alternate reason for the strong association we previously observed between circulating androgens and inflammation in PCOS. Moreover, inflammation may be capable of promoting hyperandrogenism. This latter hypothesis is the focus of the translational work currently being performed in my laboratory.

4. In a recent report, a genetic association with inflammation could not be demonstrated in PCOS (J Clin Endocrinol Metab 2014, January 1 [Epub ahead of print]). How do the findings of this report relate to the findings in your paper?

Frank Gonzalez: There is a strong familial aggregation in PCOS suggestive of a genetic component. Nevertheless, a definitive genetic link has yet to be identified despite intensive research in this area during the past 15 years. The possibility that genetics plays a role in the origins of the proinflammatory state in PCOS remains controversial despite this most recent negative study. Moreover, three previous studies have reported an association between PCOS and several proinflammatory genotypes including those that encode TNF α , and the type 2 TNF receptor as well as IL-6 and its signal transducer.

Most importantly, the recent negative study could not rule out an epigenetic origin for inflammatory gene dysregulation in PCOS. Animal data showing that the PCOS phenotype occurs after prenatal androgenization coupled with a recent report that placental tissue of women with PCOS exhibits enzyme alterations favoring androgen production that may reach the fetus suggests an epigenetic origin of the disorder.

Our study that highlights the ability of hyperandrogenism to alter immune function in a fashion that can lead to downstream metabolic aberration raises the question whether fetal access to excess androgens culminates in epigenetic immune alteration. Thus, it is attractive to consider the possibility that hyperandrogenism is the progenitor of nutrient-induced inflammation. Clearly, more work needs to be done in this area. These are exciting times and the joining of forces from investigators with varied expertise could prove useful in solving the “epigenetic code”.