1 **Polycystic Ovary Syndrome as an Endogenous Alcoholic Polycystic Ovary**

2 **Syndrome**

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25 **ABSTRACT**

26

27 Polycystic ovary syndrome (PCOS) is a growing worldwide public health problem that

28 affects millions of women in their reproductive age. Despite being a very common

29 disorder among women, there are still gaps regarding knowledge of disease

30 mechanisms. In this respect, it was recently reported that acetaldehyde (ACD) is

31 endogenously formed during normal ovarian steroidogenesis. The researchers

32 demonstrated that in physiological concentrations ACD caused no detrimental effect on

33 ovarian tissue. Contrariwise, in supraphysiological levels, ACD impairs granulosa cell

34 differentiation, reduces ovulation, and decreases oocyte quality. Gut microbiota of

35 patients with nonalcoholic fatty liver disease (NAFLD) produces significant quantities

36 of endogenous ethanol (EE) and ACD. Because PCOS is closely linked to NAFLD, an

37 ethanol-producing disorder, we hypothesize that it can be an endogenous alcoholic

38 polycystic ovary syndrome (EAPCOS). The main findings of this study were that (i) the

39 odds ratio of having polycystic ovaries is 30-fold greater in alcohol-exposed women

40 than among unexposed controls; (ii) NAFLD/PCOS patients produce gonadotoxic

41 quantities of EE; (iii) NAFLD/PCOS and alcoholic hepatitis individuals share similar

42 liver expression levels of genes regulating high-km ethanol-metabolizing enzymes; (iv)

43 NAFLD/PCOS and alcohol-tolerant drinkers share similar high-capacity to metabolize

44 ethanol in the gut-liver axis; and (v) low blood alcohol concentration (BAC) in

45 NAFLD/PCOS and alcohol-tolerant individuals stem from extensive alcohol

46 degradation in gut-liver axis and significant fecal loss of ethanol. In summary, we

47 provide mechanistic insights supporting the hypothesis that PCOS can be indeed an

48 EAPCOS.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility in women over its reproductive lifetime [1]. Available data indicate that PCOS is closely linked to obesity, insulin resistance, and nonalcoholic fatty liver disease (NAFLD) [2,3]. This suggests that these conditions share a common etiological background.

A striking feature of patients with NAFLD and, by extension with PCOS, is to produce significantly more endogenous ethanol (EE) than controls [4–6]. Accordingly, it is believed that EE plays a critical role in NAFLD development and progression [7–9]. From these observations, we hypothesize that EE also may play a causative role in PCOS pathogenesis.

It is no novelty the intriguing idea about the existence of an endogenous alcoholic disease. Early researchers attempting to validate this hypothesis have provided disappointing results. This discouraged further investigation regarding this matter for several decades. Firstly, because blood-alcohol concentration (BAC) following jejunoileal bypass was significantly lower than in alcoholics, it was concluded that the quantity of EE was insufficient to elicit liver injury [10]. Secondly, since liver histology was normal in a rat model of small intestinal bacterial overgrowth (SIBO), it was inferred that gut bacteria are unable to produce hepatotoxic amounts of ethanol [11]. However, Sprague-Dawley strains only develop steatohepatitis and fibrosis 12 to14 weeks after study initiation. And in this study, the rodents were sacrificed very early, around the 4th to 5th weeks of experimentation [12]. Therefore, as this mouse model recapitulates the histopathological spectrum of human alcoholic liver disease, we postulate that it can also cause polycystic ovaries.

73   Thus, the main focus of this study was to provide a mechanistic explanation of how

74   PCOS may be an endogenous alcoholic polycystic ovary syndrome (EAPCOS).

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Ethanol is a prodrug

As a prodrug, ethanol requires conversion to ACD in order to exert its cytotoxic properties [13,14]. This pharmacokinetic characteristic of ethanol is of paramount importance for a mechanistic understanding of the EAPCOS hypothesis. The clear and obvious implication of this is that in a scenario of extensive presystemic catabolism of ethanol, BACs can be negligible or even undetectable. The finding that intravenous infusion of cirrhotogenic amounts of ethanol (57.6 to 115.2 g/d) in alcohol-tolerant drinkers induces only modest BACs (1.5 to 4.5 mg/dL) supports this notion [15].

Gastrointestinal production and degradation of ethanol

Gastrointestinal microbiota of healthy subjects produces nontoxic amounts of EE from luminal dietary carbohydrates. Next, EE is absorbed and metabolized in the liver to ACD, which in turn is oxidized to non-toxic amounts of acetate [16]. In contrast, in SIBO-related conditions such as NAFLD/PCOS [17][18] and malabsorption syndromes [19], gut production of EE is significantly greater than in controls [4–6]. Agreeing with this, gut/fecal concentrations of EE in these cases are proportionally equal to or even greater than those obtained after moderate drinking [19–21]As ethanol is formed within a dysbiotic gut, it is converted to ACD in a dose- and concentration-dependent manner [11]. In this setting, ACD-producing alcohol dehydrogenase (ADH) activity is higher than that of ACD-oxidizing aldehyde dehydrogenase (ALDH) [22]. The net result is ACD build-up coupled with low BACs. However, in the auto-brewery syndrome, massive production of EE exceeds gut-liver axis ability to clear alcohol from circulation. As a consequence, BAC may reach 250-350 mg/dL [23].

115   Blind-loop contents of rat jejunum converts ethanol to ACD at a rate of 1.99 µM/min •

116   mL under aerobic conditions [11]. If applicable to patients with SIBO and small bowel

117   contents around 2000 mL, it is estimated that everyone can convert ~528 g of EE into

118   ACD daily. Experimentally it has been demonstrated that extrahepatic ACD is 30 to

119   330-fold more hepatotoxic than that formed intrahepatically [24,25]. Extrapolating this

120   to humans, 0.18-2 g of EE will provide an amount of ACD as hepatotoxic as that

121   generated intrahepatically from a cirrhotogenic dose of 60 g ethanol [26].

122   BACs found in NAFLD/PCOS as well as in alcohol-tolerant subjects are consistently

123   low [15,27]. In this scenario, for maintaining a steady-state BAC of 7.14 mg/dL [27]

124   NAFLD/PCOS patients would need a 24-h continuous intravenous infusion of ethanol

125   at a rate ~9.5 g/h (228 g/day) [28].

126   Lastly, a seminal study showed up-regulation of all genes involved in ethanol

127   metabolism in nonalcoholic steatohepatitis livers [5]. Importantly, these genes encode

128   enzymes those maximal catalytic activities are at high ethanol concentrations [29]. Even

129   more noteworthy is the finding that hepatic expression of ethanol-metabolizing genes in

130   NAFLD/PCOS is similar to that of alcoholic hepatitis [7].

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132   **Ethanol pharmacokinetics in NAFLD/PCOS is similar to that of alcohol-tolerant**

133   **individuals**

134   Blood-alcohol elimination rate may be 3-fold to 4-fold higher in alcohol-tolerant than in

135   healthy individuals and social drinkers [29]. Causative factors include induction of

136   high-Km alcohol-metabolizing enzymes by ethanol, insulin resistance, ketone bodies,

137   unsaturated fatty acids [30], iron overload [31], hyperglycemia [32], and gut microbial

138   degradation of ethanol [11]. Additionally, genetic polymorphisms of alcohol-

139   metabolizing enzymes play an essential role in the development of this so-called alcohol

140   tolerance/adaptation process [33,34]. In this setting, instead of metabolizing ethanol in

141   milligram levels through ADH1 activity, the individual starts doing this at tens of grams

142   scale via CYP2E1, catalase, ADH3, and ADH4 [30,35–37]For example, for maintaining

143   a steady-state BAC between 1.5 to 4.5 mg/dL, alcohol-tolerant individuals require a

144   continuous intravenous infusion of ethanol at a rate equivalent to 57.6 to 115.2 g/d [15].

145   Interestingly, and probably not by chance, all these risk factors for increased blood-

146   alcohol clearance are also present in NAFLD/PCOS [5,38–40]. For this reason, it is

147   intuitive to infer that patients with NAFLD/PCOS metabolize exogenous/endogenous

148   ethanol similarly to alcohol-tolerant individuals (Figure). In line with this argument, (i)

149   aberrant microbiota found in NAFLD as well as in alcoholics consists of both ethanol-

150   producing and -degrading bacteria [4,41,42], (ii) gut production and degradation of

151   ethanol are dose-dependent and simultaneous processes that prevent high BAC

152   [11,19,43,44], and (iii) gut concentrations of ACD reach mutagenic values (49-87 µM)

153   in rat blind loops [11]. Furthermore, impaired gastrointestinal absorption [45–48] and

154   binding/entrapment of alcohol in food constituents certainly contribute to low BACs

155   [47,49]. Notably, fecal loss of ethanol reaches concentration values up to 50-fold greater

156   than BACs found in NAFLD [19][27].

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158   **Calculating EE production from a standard human pharmacokinetic model**

159   One study showed that average BAC of twenty patients with NAFLD was 7.14 mg/dL

160   after a 12h overnight fast [27]. Assuming that ethanol elimination rate of these

161   individuals was 20 mg/dL/h and that its mean height was 1.74 m, we estimate the

162   amount of EE produced by each patient. To achieve this, we use a validated

163 physiologically-based model of alcohol metabolism, which has been described in detail

164 elsewhere [28]. According to our calculations, each patient produced 161.49 g of EE

165 after a 12-h overnight fast. By extrapolating the data to three equicaloric meals, the

166 daily production of EE should reach 484 g. Because EE undergoes extensive conversion

167 to ACD in the gut-liver axis, estimated total circulating alcohol burden is only 4.6 g.

168 This leads to the characteristically low BAC found in these patients (see [28] for

169 equations and calculation procedures).

Ovariotoxicity of ethanol

171 It has been shown that endogenous ACD is formed as a byproduct during normal

172 ovarian steroidogenesis [50]. In this situation, there is no ovotoxicity because it

173 converted to acetate by ovarian ALDH. On the contrary, in supraphysiological

174 concentrations, ACD disrupts the differentiation of granulosa cells, reduces ovulation

175 and lowers oocyte quality [50]. Acute as well as chronic exposure to ethanol inhibits

176 ovarian steroidogenic acute regulatory protein (StAR), which plays a crucial role in

177 gonadotropin-stimulated gonadal hormone production [51,52]. This leads to an increase

178 in the number of the corpora lutea, atretic follicles, regression of theca antral follicles,

179 vacuolation/fat deposition in granulosa, theca, and interstitial cells [53]. As a result,

180 alcohol exposure entails disruption of puberty and menstrual cycling as well as a

181 hormonal imbalance in pre and postmenopausal women [54].

182 Agreeing with these observations, the odds ratio of having PCOS is about 30-fold

183 higher among Chinese women consuming alcohol than in matched controls [55]. This

184 substantial discrepancy is because 30% to 40% of Asian individuals carry out a

185 defective ALDH2 enzyme, providing the accumulation of very high quantities of ACD

186 [56,57]. Moreover, subgroup analyses of multiple subpopulations suggest a positive

187   relationship between heavy alcohol intake and ovarian cancer [58]. Supporting

188   argument for this epidemiological connection comes from the finding of elevated

189   concentrations of ACD in ovarian cancer tissues [59].

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191   **Other endogenous and exogenous risk factors for PCOS**

192   According to the data presented here, ethanol itself recapitulates the entire phenotype of

193   PCOS. However, other endogenous/exogenous toxins may be implicated in its

194   pathogenesis. These include dicarbonyl compounds [60–62], advanced glycation end

195   products (AGEs) [63,64], advanced lipid peroxidation end products (ALEs) [65,66] and

196   nitric oxide radicals [67]. Furthermore, it is possible that epigenetic changes and

197   aberrant microRNA (miRNA) may play a relevant role in PCOS development [68,69].

198   Considering that NAFLD/PCOS is an alcohol-producing disorder, we postulate that

199   even alcohol-abstinent women are at increased risk of developing ovarian cancer. This

200   event would be particularly likely among NAFLD/PCOS patients carrying genetic

201   susceptibility to both sporadic and hereditary ovarian neoplasms [70,71]. Likewise,

202   NAFLD/PCOS women carrying functional polymorphisms in ethanol-metabolizing

203   genes may be at highest risk for developing ovarian cancer and other alcohol-related

204   neoplasms [72,73].

205

206   **Conclusion**

207   In short, our data reconcile the apparently contradictory association between exposure to

208   large amounts of ethanol concurrently with negligible BACs [15]. The EAPCOS

209   hypothesis contains several limitations, including the fact that most of the evidence

210   comes from uncontrolled observational studies. Nevertheless, it provides sufficient

211   evidence justifying the existence of an EAPCOS. Lastly, if confirmed by further studies,

212   our hypothesis may contribute to novel therapeutic and preventive strategies for disease

213   management and control.

214

215   Author's roles

216   I.C.M. elaborated the study's hypothesis and purpose, performed the literature search,

217   wrote and critically reviewed and approved the final version of the paper; J.G.L.

218   contributed to the study design, figure elaboration, paper editing, and critically reviewed

219   and approved the final version of the manuscript.

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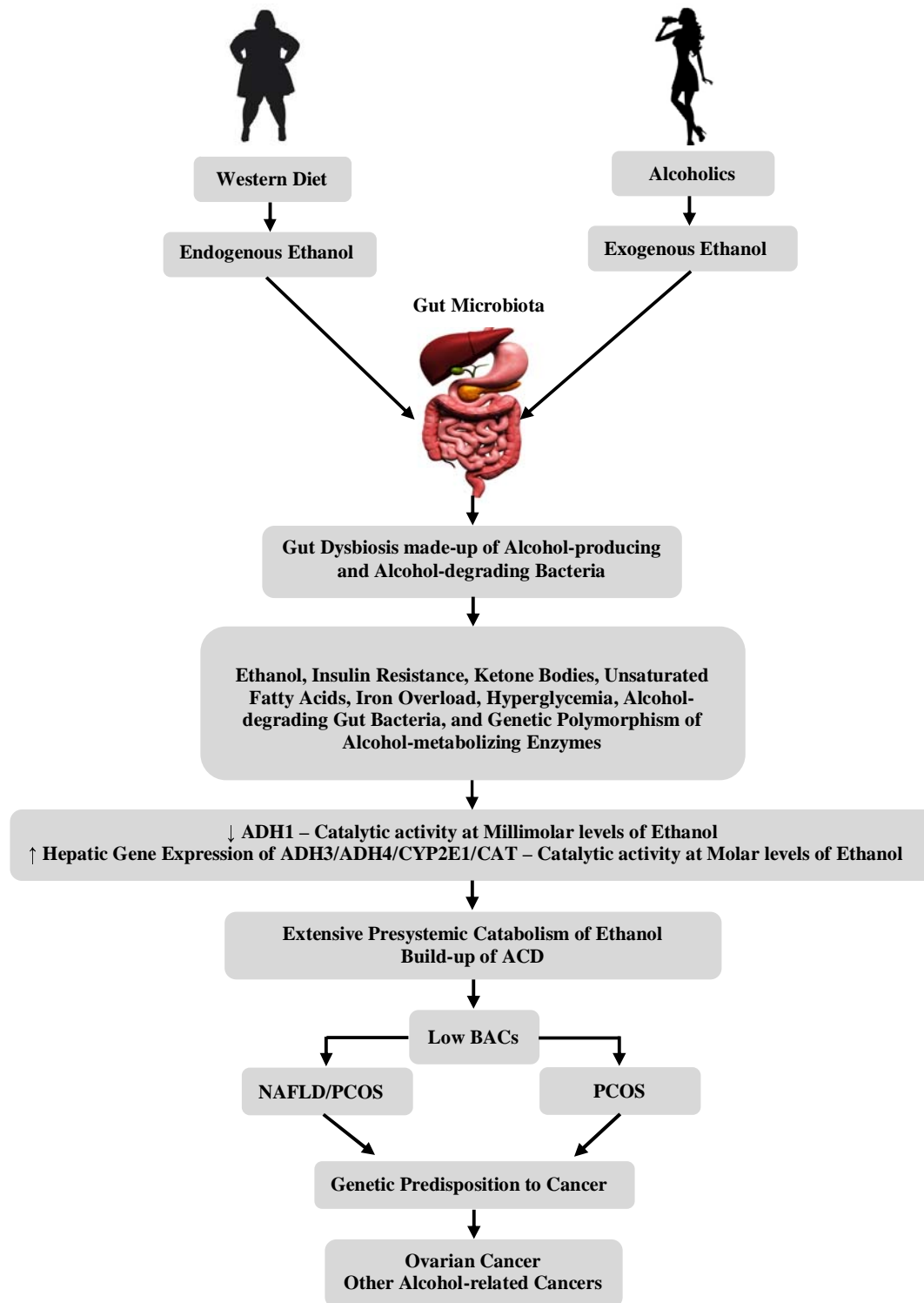458   identified genes associated with ovarian cancer progression. Int J Oncol

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Figure 1. Evidence that NAFLD/PCOS patients metabolize etanol similarly to Alcohol-tolerant individuals. Chronic exposure either to endogenous or exogenous high ethanol concentrations leads to a gut dysbiosis made-up of alcohol-producing and –degrading organisms. Then, a number of metabolic alterations switch alcohol metabolism from milligram

scale to hundreds of grams per day. This extensive presystemic clearance of ethanol causes ACD build-up, which in turn leads to the consistently low BACs. Lastly, in genetically predisposed women carcinogenic ACD can lead to ovarian cancer and other alcohol-related neoplasms. Km = Michaelis Constant; ADH = Alcohol dehydrogenase; CYP2E1 = Cytochrome P-450 2-E1; CAT = Catalase; EAPCOS = Endogenous Alcoholic Polycystic Ovary Syndrome; PCOS = Polycystic Ovary Syndrome; ACD = Acetaldehyde;