Polycystic Ovary Syndrome as an Endogenous Alcoholic Polycystic Ovary Syndrome

¹Medeiros IC. (Ivanildo Coutinho de Medeiros, MD), ²Lima JG. (Josivan Gomes de Lima, MD)

Universidade Federal do Rio Grande do Norte, Departamento de Medicina Clínica,
¹Divisão de Gastroenterologia e ²Divisão de Endocrinologia – Av. Nilo Peçanha, 620 -
 Natal/RN, Brazil

Correspondence to: Ivanildo Coutinho de Medeiros

Rua Hist. Tobias Monteiro, 1863 – Lagoa Nova

Natal-RN, Brazil - CEP 59056-120

Phone: +55 84 9984-3994

Fax: +55 84 3342-9703

Author email: coutimed@gmail.com

Co-author email: josivanlima@gmail.com

Financial Support

This manuscript has no financial support.

ABSTRACT

Polycystic ovary syndrome (PCOS) is a growing worldwide public health problem that affects millions of women in their reproductive age. Despite being a very common disorder among women, there are still gaps regarding knowledge of disease mechanisms. In this respect, it was recently reported that acetaldehyde (ACD) is endogenously formed during normal ovarian steroidogenesis. The researchers demonstrated that in physiological concentrations ACD caused no detrimental effect on ovarian tissue. Contrariwise, in supraphysiological levels, ACD impairs granulosa cell differentiation, reduces ovulation, and decreases oocyte quality. Gut microbiota of patients with nonalcoholic fatty liver disease (NAFLD) produces significant quantities of endogenous ethanol (EE) and ACD. Because PCOS is closely linked to NAFLD, an ethanol-producing disorder, we hypothesize that it can be an endogenous alcoholic polycystic ovary syndrome (EAPCOS). The main findings of this study were that (i) the odds ratio of having polycystic ovaries is 30-fold greater in alcohol-exposed women than among unexposed controls; (ii) NAFLD/PCOS patients produce gonadotoxic quantities of EE; (iii) NAFLD/PCOS and alcoholic hepatitis individuals share similar liver expression levels of genes regulating high-km ethanol-metabolizing enzymes; (iv) NAFLD/PCOS and alcohol-tolerant drinkers share similar high-capacity to metabolize ethanol in the gut-liver axis; and (v) low blood alcohol concentration (BAC) in NAFLD/PCOS and alcohol-tolerant individuals stem from extensive alcohol degradation in gut-liver axis and significant fecal loss of ethanol. In summary, we provide mechanistic insights supporting the hypothesis that PCOS can be indeed an EAPCOS.

49

INTRODUCTION

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

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

60 It is no novelty the intriguing idea about the existence of an endogenous alcoholic
61 disease. Early researchers attempting to validate this hypothesis have provided
62 disappointing results. This discouraged further investigation regarding this matter for
63 several decades. Firstly, because blood-alcohol concentration (BAC) following
64 jejunoileal bypass was significantly lower than in alcoholics, it was concluded that the
65 quantity of EE was insufficient to elicit liver injury [10]. Secondly, since liver histology
66 was normal in a rat model of small intestinal bacterial overgrowth (SIBO), it was
67 inferred that gut bacteria are unable to produce hepatotoxic amounts of ethanol [11].
68 However, Sprague-Dawley strains only develop steatohepatitis and fibrosis 12 to 14
69 weeks after study initiation. And in this study, the rodents were sacrificed very early,
70 around the 4th to 5th weeks of experimentation [12]. Therefore, as this mouse model
71 recapitulates the histopathological spectrum of human alcoholic liver disease, we
72 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).

75

76

77

78

79

80

81

82

83

84

85

86

87

88

89

90

91

92 **Ethanol is a prodrug**

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

100

101 **Gastrointestinal production and degradation of ethanol**

102 Gastrointestinal microbiota of healthy subjects produces nontoxic amounts of EE from
103 luminal dietary carbohydrates. Next, EE is absorbed and metabolized in the liver to
104 ACD, which in turn is oxidized to non-toxic amounts of acetate [16]. In contrast, in
105 SIBO-related conditions such as NAFLD/PCOS [17][18] and malabsorption syndromes
106 [19], gut production of EE is significantly greater than in controls [4–6]. Agreeing with
107 this, gut/fecal concentrations of EE in these cases are proportionally equal to or even
108 greater than those obtained after moderate drinking [19–21] As ethanol is formed within
109 a dysbiotic gut, it is converted to ACD in a dose- and concentration-dependent manner
110 [11]. In this setting, ACD-producing alcohol dehydrogenase (ADH) activity is higher
111 than that of ACD-oxidizing aldehyde dehydrogenase (ALDH) [22]. The net result is
112 ACD build-up coupled with low BACs. However, in the auto-brewery syndrome,
113 massive production of EE exceeds gut-liver axis ability to clear alcohol from
114 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 $\mu\text{M}/\text{min} \cdot$
 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 whose 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].

131

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- K_m 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 μ M)
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].

157

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).

170 **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].

190

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.

220

221

222

223

224

225

226

227

228

229

230 REFERENCES

- 231 [1] Costello MF, Ledger WL. Evidence-based lifestyle and pharmacological
232 management of infertility in women with polycystic ovary syndrome. *Womens*
233 *Health (Lond Engl)* 2012;8:277–90. doi:10.2217/whe.12.14.
- 234 [2] Baranova A, Tran TP, Bireddi A, Younossi ZM. Systematic review: association
235 of polycystic ovary syndrome with metabolic syndrome and non-alcoholic fatty
236 liver disease. *Aliment Pharmacol Ther* 2011;33:801–14. doi:10.1111/j.1365-
237 2036.2011.04579.x.
- 238 [3] Ollila M-M, Piltonen T, Puukka K, Ruokonen A, Järvelin M-R, Tapanainen JS,
239 et al. Weight Gain and Dyslipidemia in Early Adulthood Associate with
240 Polycystic Ovary Syndrome: Prospective Cohort Study. *J Clin Endocrinol Metab*
241 2015;101:jc20153543. doi:10.1210/jc.2015-3543.
- 242 [4] Zhu L, Baker SS, Gill C, Liu W, Alkhouri R, Baker RD, et al. Characterization of
243 gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection
244 between endogenous alcohol and NASH. *Hepatology* 2013;57:601–9.
245 doi:10.1002/hep.26093.
- 246 [5] Baker SS, Baker RD, Liu W, Nowak NJ, Zhu L. Role of alcohol metabolism in
247 non-alcoholic steatohepatitis. *PLoS One* 2010;5:e9570.
248 doi:10.1371/journal.pone.0009570.
- 249 [6] Nair S, Cope K, Risby TH, Diehl AM, Terence RH. Obesity and female gender
250 increase breath ethanol concentration: potential implications for the pathogenesis
251 of nonalcoholic steatohepatitis. *Am J Gastroenterol* 2001;96:1200–4.
252 doi:10.1111/j.1572-0241.2001.03702.x.

- 253 [7] Zhu R, Baker SS, Moylan CA, Abdelmalek MF, Guy CD, Zamboni F, et al.
254 Systematic Transcriptome Analysis Reveals Elevated Expression of Alcohol
255 Metabolizing Genes in NAFLD Livers. J Pathol 2015;238:531–42.
256 doi:10.1002/path.4650.
- 257 [8] Aljomah G, Baker SS, Liu W, Kozielski R, Oluwole J, Lupu B, et al. Induction
258 of CYP2E1 in non-alcoholic fatty liver diseases. Exp Mol Pathol 2015;99:677–
259 81. doi:10.1016/j.yexmp.2015.11.008.
- 260 [9] Aljomah G, Baker SS, Liu W, Kozielski R, Baker RD, Zhu L. Genes of Alcohol
261 Metabolism in Patients With Simple Steatosis and NASH. Gastroenterology
262 2015;146:S-763-S-764. doi:10.1016/S0016-5085(14)62759-1.
- 263 [10] Mezey E, Imbembo AL, Potter JJ, Rent KC, Lombardo R, Holt PR. Endogenous
264 ethanol production and hepatic disease following jejunoileal bypass for morbid
265 obesity. Am J Clin Nutr 1975;28:1277–83.
- 266 [11] Baraona E, Julkunen R, Tannenbaum L, Lieber CS. Role of intestinal bacterial
267 overgrowth in ethanol production and metabolism in rats. Gastroenterology
268 1986;90:103–10.
- 269 [12] Lichtman SN, Sartor RB, Keku J, Schwab JH. Hepatic inflammation in rats with
270 experimental small intestinal bacterial overgrowth. Gastroenterology
271 1990;98:414–23.
- 272 [13] Faut M, Rodríguez de Castro C, Bietto FM, Castro JA, Castro GD. Metabolism
273 of ethanol to acetaldehyde and increased susceptibility to oxidative stress could
274 play a role in the ovarian tissue cell injury promoted by alcohol drinking. Toxicol
275 Ind Health 2009;25:525–38. doi:10.1177/0748233709345937.

- 276 [14] Meskar A, Holownia A, Bardou LG, Menez JF. Effect of acetaldehyde generated
277 from ethanol by ADH-transfected CHO cells on their membrane fatty acid
278 profiles. Alcohol 1996;13:611–6. doi:10.1016/s0741-8329(96)00076-6.
- 279 [15] Lands WE. A review of alcohol clearance in humans. Alcohol 1998;15:147–60.
280 doi:10.1016/s0741-8329(97)00110-9.
- 281 [16] Krebs HA, Perkins JR. The physiological role of liver alcohol dehydrogenase.
282 Biochem J 1970;118:635–44. doi:10.1042/bj1180635.
- 283 [17] Ferolla SM, Armiliato GNA, Couto CA, Ferrari TCA. The Role of Intestinal
284 Bacteria Overgrowth in Obesity-Related Nonalcoholic Fatty Liver Disease.
285 Nutrients 2014;6:5583–99. doi:10.3390/nu6125583.
- 286 [18] Kapil S, Duseja A, Sharma BK, Singla B, Chakraborti A, Das A, et al. Small
287 intestinal bacterial overgrowth and toll like receptor signaling in patients with
288 nonalcoholic fatty liver disease. J Gastroenterol Hepatol 2016;31:213–21.
289 doi:10.1111/jgh.13058.
- 290 [19] Picot D, Lauvin R, Hellegouarc’h R. [Intra-digestive fermentation in intestinal
291 malabsorption syndromes: relations with elevated serum activity of gamma-
292 glutamyl-transpeptidase]. Gastroenterol Clin Biol 1997;21:562–6. doi:GCB-08-
293 1997-21-8-9-0399-8320-101019-ART71.
- 294 [20] Klipstein FA, Holdeman L V, Corcino JJ, Moore WE. Enterotoxigenic intestinal
295 bacteria in tropical sprue. Ann Intern Med 1973;79:632–41. doi:10.7326/0003-
296 4819-79-5-632.
- 297 [21] Halsted CH, Robles EA, Mezey E. Distribution of ethanol in the human
298 gastrointestinal tract. Am J Clin Nutr 1973;26:831–4.

- 299 [22] Pronko P, Bardina L, Satanovskaya V, Kuzmich A, Zimatkin S. Effect of chronic
300 alcohol consumption on the ethanol- and acetaldehyde-metabolizing systems in
301 the rat gastrointestinal tract. *Alcohol Alcohol* 2002;37:229–35.
302 doi:10.1093/alcalc/37.3.229.
- 303 [23] Dahshan A, Donovan K. Auto-brewery syndrome in a child with short gut
304 syndrome: case report and review of the literature. *J Pediatr Gastroenterol Nutr*
305 2001;33:214–5. doi:10.1097/00005176-200108000-00024.
- 306 [24] Bankowski E, Pawlicka E, Sobolewski K. Liver collagen of rats submitted to
307 chronic intoxication with acetaldehyde. *Mol Cell Biochem* 1993;121:37–43.
308 doi:10.1007/bf00928698.
- 309 [25] Matysiak-Budnik T, Jokelainen K, Kärkkäinen P, Mäkisalo H, Ohisalo J,
310 Salaspuro M. Hepatotoxicity and absorption of extrahepatic acetaldehyde in rats.
311 *J Pathol* 1996;178:469–74. doi:10.1002/(SICI)1096-
312 9896(199604)178:4<469::AID-PATH510>3.0.CO;2-9.
- 313 [26] O’Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. *Am J*
314 *Gastroenterol* 2010;105:14–32. doi:10.1038/ajg.2009.593.
- 315 [27] Menezes CN, Raal F, Immelman A, Song E. The role of increased
316 gastrointestinal alcohol production in patients with the metabolic syndrome:
317 Implications for the pathogenesis of non-alcoholic fatty liver disease. *J*
318 *Endocrinol Metab Diabetes South Africa* 2008;13:48–56.
319 doi:10.1080/22201009.2008.10872170.
- 320 [28] Medeiros IC de, de Lima JG. Is nonalcoholic fatty liver disease an endogenous
321 alcoholic fatty liver disease? - A mechanistic hypothesis. *Med Hypotheses*

- 2015;85:148–52. doi:10.1016/j.mehy.2015.04.021.
- [29] Cederbaum AI. Alcohol metabolism. Clin Liver Dis 2012;16:667–85.
doi:10.1016/j.cld.2012.08.002.
- [30] Leung T-M, Nieto N. CYP2E1 and oxidant stress in alcoholic and non-alcoholic fatty liver disease. J Hepatol 2012;58:395–8. doi:10.1016/j.jhep.2012.08.018.
- [31] Cederbaum AI. Iron and CYP2E1-dependent oxidative stress and toxicity. Alcohol 2003;30:115–20.
- [32] Swaminathan K, Kumar SM, Clemens DL, Dey A. Inhibition of CYP2E1 leads to decreased advanced glycated end product formation in high glucose treated ADH and CYP2E1 over-expressing VL-17A cells. Biochim Biophys Acta 2013;1830:4407–16. doi:10.1016/j.bbagen.2013.05.022.
- [33] Oshima S, Haseba T, Nemoto A, Siiya S, Kanda T, Ohno Y. Effect of ALDH2 Genetic Polymorphism on the Adaptive Change in Alcohol Metabolism Due to Continuous Moderate Alcohol Consumption in Humans. Food Nutr Sci 2015;6:195–204. doi:10.4236/fns.2015.62020.
- [34] Bosron WF, Li T-K. Genetic polymorphism of human liver alcohol and aldehyde dehydrogenases, and their relationship to alcohol metabolism and alcoholism. Hepatology 1986;6:502–10. doi:10.1002/hep.1840060330.
- [35] Haseba T, Ohno Y. A new view of alcohol metabolism and alcoholism--role of the high-Km Class III alcohol dehydrogenase (ADH3). Int J Environ Res Public Health 2010;7:1076–92. doi:10.3390/ijerph7031076.
- [36] Lieber CS. CYP2E1: from ASH to NASH. Hepatol Res 2004;28:1–11.

- 344 [37] Lieber CS. Alcoholic fatty liver: its pathogenesis and mechanism of progression
345 to inflammation and fibrosis. *Alcohol* 2004;34:9–19.
346 doi:10.1016/j.alcohol.2004.07.008.
- 347 [38] Yang S-L, Xia J-H, Zhang Y-Y, Fan J-G, Wang H, Yuan J, et al.
348 Hyperinsulinemia shifted energy supply from glucose to ketone bodies in early
349 nonalcoholic steatohepatitis from high-fat high-sucrose diet induced Bama
350 minipigs. *Sci Rep* 2015;5:13980. doi:10.1038/srep13980.
- 351 [39] Puri P, Wiest MM, Cheung O, Mirshahi F, Sargeant C, Min HK, et al. The
352 plasma lipidomic signature of nonalcoholic steatohepatitis. *Hepatology*
353 2009;50:1827–38. doi:10.1002/hep.23229.
- 354 [40] Birkenfeld AL, Shulman GI. Nonalcoholic fatty liver disease, hepatic insulin
355 resistance, and type 2 diabetes. *Hepatology* 2014;59:713–23.
356 doi:10.1002/hep.26672.
- 357 [41] Tsuruya A, Kuwahara A, Saito Y, Yamaguchi H, Tenma N, Inai M, et al. Major
358 Anaerobic Bacteria Responsible for the Production of Carcinogenic
359 Acetaldehyde from Ethanol in the Colon and Rectum. *Alcohol Alcohol*
360 2016;51:395–401. doi:10.1093/alcalc/agv135.
- 361 [42] Bode JC, Bode C, Heidelberg R, Durr HK, Martini GA. Jejunal microflora in
362 patients with chronic alcohol abuse. *Hepatogastroenterology* 1984;31:30–4.
- 363 [43] Jokelainen K, Matysiak-Budnik T, Mäkisalo H, Höckerstedt K, Salaspuro M.
364 High intracolonic acetaldehyde values produced by a bacteriocolonial pathway for
365 ethanol oxidation in piglets. *Gut* 1996;39:100–4. doi:10.1136/gut.39.1.100.
- 366 [44] Nosova T, Jokelainen K, Kaihovaara P, Heine R, Jousimies-Somer H, Salaspuro

- 367 M. Characteristics of aldehyde dehydrogenases of certain aerobic bacteria
368 representing human colonic flora. *Alcohol Alcohol* 1998;33:273–80.
- 369 [45] Jackson SJ, Leahy FE, McGowan AA, Bluck LJC, Coward WA, Jebb SA.
370 Delayed gastric emptying in the obese: an assessment using the non-invasive
371 ¹³C-octanoic acid breath test. *Diabetes, Obes Metab* 2004;6:264–70.
372 doi:10.1111/j.1462-8902.2004.0344.x.
- 373 [46] Paton A. Alcohol in the body. *BMJ* 2005;330:85–7.
374 doi:10.1136/bmj.330.7482.85.
- 375 [47] Jones AW, Jönsson KA, Kechagias S. Effect of high-fat, high-protein, and high-
376 carbohydrate meals on the pharmacokinetics of a small dose of ethanol. *Br J Clin*
377 *Pharmacol* 1997;44:521–6.
- 378 [48] Roland BC, Ciarleglio MM, Clarke JO, Semler JR, Tomakin E, Mullin GE, et al.
379 Small Intestinal Transit Time Is Delayed in Small Intestinal Bacterial
380 Overgrowth. *J Clin Gastroenterol* 2015;49:571–6.
381 doi:10.1097/MCG.0000000000000257.
- 382 [49] Oshima S. Water-insoluble fractions of botanical foods lower blood ethanol
383 levels in rats by physically maintaining the ethanol solution after ethanol
384 administration. *Funct Foods Heal Dis* 2015;5:406–16.
- 385 [50] Kawai T, Mihara T, Kawashima I, Fujita Y, Ikeda C, Negishi H, et al.
386 Endogenous acetaldehyde toxicity during antral follicular development in the
387 mouse ovary. *Reprod Toxicol* 2012;33:322–30.
388 doi:10.1016/j.reprotox.2012.01.001.
- 389 [51] Srivastava VK, Hiney JK, Dearth RK, Les Dees W. Acute effects of ethanol on

- steroidogenic acute regulatory protein (StAR) in the prepubertal rat ovary.
Alcohol Clin Exp Res 2001;25:1500–5. doi:10.1097/00000374-200110000-00014.
- [52] Srivastava VK, Hiney JK, Dearth RK, Les Dees W. Chronic effects of prepubertal ethanol administration on steroidogenic acute regulatory protein in the rat ovary. Alcohol Clin Exp Res 2002;26:107–13.
- [53] Laura IA, Martinez M, Padovani CR, Martinez FE. Ultrastructural and morphometric analysis on the ovary of Wistar rats after chronic ethanol ingestion. J Submicrosc Cytol Pathol 2003;35:167–76.
- [54] Emanuele MA, Wezeman F, Emanuele N V, Ph D. Alcohol's effects on female reproductive function. Alcohol Res Heal J Natl Inst Alcohol Abus Alcohol 2002;26:274–81.
- [55] Zhang J, Liu XF, Liu Y, Xu LZ, Zhou LL, Tang LL, et al. Environmental risk factors for women with polycystic ovary syndrome in china: a population-based case-control study. J Biol Regul Homeost Agents 2014;28:203–11.
- [56] Ginsberg G, Smolenski S, Hattis D, Sonawane B. Population distribution of aldehyde dehydrogenase-2 genetic polymorphism: implications for risk assessment. Regul Toxicol Pharmacol 2002;36:297–309.
- [57] Brooks PJ, Zakhari S. Acetaldehyde and the genome: Beyond nuclear DNA adducts and carcinogenesis. Env Mol Mutagen 2013. doi:10.1002/em.21824.
- [58] Yan-Hong H, Jing L, Hong L, Shan-Shan H, Yan L, Ju L. Association between alcohol consumption and the risk of ovarian cancer: a meta-analysis of prospective observational studies. BMC Public Health 2015;15:223.

- 413 doi:10.1186/s12889-015-1355-8.
- 414 [59] Orywal K, Jelski W, Zdrodowski M, Szmitkowski M. The activity of class I, II,
415 III and IV alcohol dehydrogenase isoenzymes and aldehyde dehydrogenase in
416 ovarian cancer and ovarian cysts. Adv Med Sci 2013;58:19–23. doi:10.2478/ams-
417 2013-0012.
- 418 [60] Tatone C, Eichenlaub-Ritter U, Amicarelli F. Dicarbonyl stress and glyoxalases
419 in ovarian function. Biochem Soc Trans 2014;42:433–8.
420 doi:10.1042/BST20140023.
- 421 [61] Chaplen FW, Fahl WE, Cameron DC. Evidence of high levels of methylglyoxal
422 in cultured Chinese hamster ovary cells. Proc Natl Acad Sci U S A
423 1998;95:5533–8.
- 424 [62] Tucker JD, Taylor RT, Christensen ML, Strout CL, Hanna ML, Carrano A V.
425 Cytogenetic response to 1,2-dicarbonyls and hydrogen peroxide in Chinese
426 hamster ovary AUXB1 cells and human peripheral lymphocytes. Mutat Res
427 Toxicol 1989;224:269–79. doi:10.1016/0165-1218(89)90166-3.
- 428 [63] Rutkowska AZ, Diamanti-Kandarakis E. Polycystic ovary syndrome and
429 environmental toxins. Fertil Steril 2016;106:948–58.
430 doi:10.1016/j.fertnstert.2016.08.031.
- 431 [64] Rutkowska AZ, Diamanti-Kandarakis E. Do Advanced Glycation End Products
432 (AGEs) Contribute to the Comorbidities of Polycystic Ovary Syndrome (PCOS)?
433 Curr Pharm Des 2016.
- 434 [65] Zhang J, Zhang Y, Liu H, Bai H, Wang Y, Jiang C, et al. Antioxidant properties
435 of high-density lipoproteins are impaired in women with polycystic ovary

- 436 syndrome. Fertil Steril 2015;103:1346–54. doi:10.1016/j.fertnstert.2015.02.024.
- 437 [66] Iborra A, Palacio JR, Martínez P. Oxidative stress and autoimmune response in
438 the infertile woman. Chem Immunol Allergy 2005;88:150–62.
439 doi:10.1159/000087832.
- 440 [67] Murri M, Luque-ramírez M, Insenser M, Ojeda-ojeda M, Escobar-morreale HF.
441 Circulating markers of oxidative stress and polycystic ovary syndrome (pcos): A
442 systematic review and meta-analysis. Hum Reprod Update 2013;19:268–88.
443 doi:10.1093/humupd/dms059.
- 444 [68] Ilie IR, Georgescu CE. Polycystic Ovary Syndrome-Epigenetic Mechanisms and
445 Aberrant MicroRNA. Adv. Clin. Chem., vol. 71, 2015, p. 25–45.
446 doi:10.1016/bs.acc.2015.06.001.
- 447 [69] Xu N, Kwon S, Abbott DH, Geller DH, Dumesic DA, Azziz R, et al. Epigenetic
448 mechanism underlying the development of polycystic ovary syndrome (PCOS)-
449 like phenotypes in prenatally androgenized rhesus monkeys. PLoS One
450 2011;6:e27286. doi:10.1371/journal.pone.0027286.
- 451 [70] Braem MG, Schouten LJ, Peeters PH, van den Brandt PA, Onland-Moret NC.
452 Genetic susceptibility to sporadic ovarian cancer: a systematic review. Biochim
453 Biophys Acta 2011;1816:132–46. doi:10.1016/j.bbcan.2011.05.002.
- 454 [71] Toss A, Tomasello C, Razzaboni E, Contu G, Grandi G, Cagnacci A, et al.
455 Hereditary Ovarian Cancer: Not Only BRCA 1 and 2 Genes. Biomed Res Int
456 2015;2015:341723. doi:10.1155/2015/341723.
- 457 [72] Liu X, Gao Y, Zhao B, Li X, Lu YI, Zhang J, et al. Discovery of microarray-
458 identified genes associated with ovarian cancer progression. Int J Oncol

459 2015;46:2467–78. doi:10.3892/ijo.2015.2971.

460 [73] Boffetta P, Hashibe M. Alcohol and cancer. *Lancet Oncol* 2006;7:149–56.

461 doi:10.1016/S1470-2045(06)70577-0.

462

463

Figure 1. Evidence that NAFLD/PCOS patients metabolize ethanol 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;