Indian J. Applied & Pure Bio. Vol. 39(1), 345-357 (2024). **ISSN: 0970-2091**
A Web of Science Journal

Effects of alcohol consumption on the Adrenal, Gonad and Pancreas, with special reference to the Hormonal Axis

Joydeep Das

Assistant Professor, Department of Zoology, Dinabandhu Andrews College,
Kolkata-700047 (India)
(Affiliated to University of Calcutta)
Email. Id*: joydeepdas914@gmail.com*

Abstract

The endocrine system ensures a proper communication between various organs of the body to maintain a constant internal environment. The body's ability to respond and correctly deal with changes in the internal or external environments, such as responding to stress and injury, is made possible in large part by the endocrine system. Communication between the endocrine system and the neurological and immunological systems aids these endocrine system processes to maintain bodily homeostasis. Alcohol has the ability to penetrate almost all body tissues and organs, leading to organ dysfunction and tissue damage. There is a lot of evidence to suggest that alcohol consumption causes clinical problems in the endocrine system, one of the most vital systems in the body. This system is crucial for maintaining a continuous internal environment because it promotes optimal communication between various organs and interfaces with the immunological and nervous systems. The hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-gonadal axis, as well as additional sources of hormones including the endocrine pancreas and endocrine adipose tissue, are all parts of the endocrine system. Alcohol abuse disrupts all of these systems and causes hormonal disturbances that may result in various disorders, such as stress intolerance, reproductive dysfunction, immune abnormalities, and psychological and behavioural disorders. The results of studies on both humans and animals that offer reliable evidence of the varied consequences of alcohol abuse on the endocrine system are summarised in this review. Thus, the objectives of my study are focused on the adverse effects of alcohol on different endocrine glands and human awareness of alcoholism, with a special emphasis on stress, diabetes, and reproductive health.

Key words : Hypothalamus, Pituitary, Endocrine, Hormone, Reproduction.

Alcoholism has consistently held its place among the world's risk factors for diseases that can be prevented throughout history. 5.3% of all fatalities globally in 2016 were attributed to problematic alcohol use, according to a WHO report[19]. Alcohol's impact on the functioning of the brain ranges from mild and anxiolytic disinhibitory effects, motor in coordination, sedation, emesis, amnesia, hypnosis and ultimately unconsciousness[21]. Alcohol-related deaths, diseases and disabilities are much higher in men than women and are highest in developed countries, where they range from 8%-18% for males and 2%-4% for females. According to the National Institute of Alcohol Abuse and Alcoholism, each year, approximately 80,000 people die from alcohol-related causes, making it the third leading cause of death in the United States. Approximately 14 million of Americans (7.4%) have an alcohol use disorder that is classified as either alcoholism (alcohol dependency) or alcohol abuse[49]. Numerous susceptibility genes are connected to vulnerability and risk of developing alcohol-related illnesses, as shown by human genome-wide association studies of people with a family history of alcoholism and twin studies. According to twin studies, the heritability of alcohol consumption ranges from 50 to 60%. Though intricate gene-to-gene and gene-to-environment interactions result in a variety of addiction phenotypes, alcoholism is a multifactorial and polygenic condition. Environmental factors play an equally important role in the development of alcohol-related disorders, i.e. stressful life events have been shown to influence alcohol drinking and relapse behaviours[6]. Excessive alcohol drinking has been recognized as having several adverse health consequences. Heavy alcohol drinking increases the risk of cardiovascular[17] and liver disease[34], metabolic disturbances[7] nutritional deficiencies, cancers (*i.e.* mouth, stomach, colon, liver and breast cancer), neurobiological disorders and fetal abnormalities. In contrast to heavy alcohol use, light to moderate drinking, especially of alcoholic beverages rich in polyphenols such as red wine, was reported to lower the risk of coronary heart disease, stroke and osteoporosis[24]. In this article, we will discuss some of the literature surrounding studies done in humans and animal models regarding the effects of both acute and chronic alcohol consumption on one of the body's most important systems, the endocrine system. The uniqueness of this study is that it covers the effects of alcohol on different endocrine systems. This review article aims to focus on the adverse effects of alcohol on human health, especially stress, diabetes, and reproduction.

The Endocrine system :

Along with the nervous system, the endocrine system ensures a proper communication between various organs of the body to maintain a constant internal environment, also called homeostasis. The nervous system allows rapid transmission of information between different body regions, whereas, the endocrine system, which is a complex system of glands that produce and secrete hormones directly into the blood circulation, have longer lasting actions. Substance abuse, such as chronic alcohol consumption was shown to have serious adverse effects on the different components of the endocrine system. Alcohol's effects induce hormonal disturbances that lead to profound and serious consequences at physiological and behavioural levels[40]. These

alcohol-induced hormonal deregulations affect the entire body and can result in various disorders such as cardiovascular diseases, reproductive deficits, immune dysfunction, certain cancers, bone disease and psychological and behavioural disorders.

The goal in this review is to discuss the effects of both acute and chronic alcohol exposures on the different components of the endocrine system. This study summarize the findings from human and animal studies that provide consistent evidence on the various effects of alcohol abuse on the endocrine system and on how the latter might have a role in the initiation, the development and the maintenance of alcohol drinking disorders and relapse. The hypothalamic-pituitary axis, the main hormonal centre of the endocrine system, is first discussed in this study, along with the effects of alcohol consumption on its various components, including the adrenal axis (also known as the HPA axis), gonadal axis (also known as the HPG axis), and thyroid axis (also known as the HPT axis)[20]. In addition, this paper reviews the function of the HPA axis in alcohol dependence and alcohol seeking behaviour and discusses how alcohol use affects the HPA axis' activity. Second, this overview of new literature discusses how alcohol affects pancreatic function, circadian rhythm, and body growth. Lastly, and since it is currently well documented that there is an overlap between the endocrine and the immune systems, we will discuss how deregulation in the hypothalamic-pituitary axis can negatively impact the body's immune response.

Effect of alcohol on hypothalamic-pituitary-Adrenal Axis (Hpa Axis) :

A. Normal functioning of the HPA Axis:

One of the endocrine systems that is most susceptible to the consequences of alcohol misuse is the HPA axis (Fig. 1). This hormone system governs the body's physiological activities, including immunological, metabolic, and cardiovascular processes, as well as the stress-response pathways. It combines psychological and physical inputs to help the body stay in a state of homeostasis. Neurons in the hypothalamic PVN produce and release CRF and AVP in response to stress (*i.e.*, psychological, physical, or infectious stresses) or other homeostatic difficulties. Proopiomelanocortin (POMC), a peptide, is synthesised and secreted by certain cells (*i.e.,* corticotropic cells) at the anterior pituitary when CRF binds to CRF1 receptors there. ACTH, -endorphin (BEP), and three related peptides known as an -melanocyte stimulating hormones can all be broken down into smaller peptides by POMC [26]. ACTH is predominantly created by the anterior pituitary's processing of POMC, whereas BEP is primarily obtained from POMC produced in the hypothalamus' ventromedial arcuate nucleus. The effects of CRF on ACTH synthesis in the anterior pituitary are potentiated by the AVP's binding to V1b receptors concurrently.

Then, ACTH is released into the bloodstream, where it attaches to particular receptors on cells in the zona fasciculata of the cortex of the adrenal glands, which are found on top of the kidneys. These receptors are melanocortin type 2 receptors. Glucocorticoid hormones, primarily cortisol in humans and corticosterone in rodents, are stimulated there by ACTH. These hormones

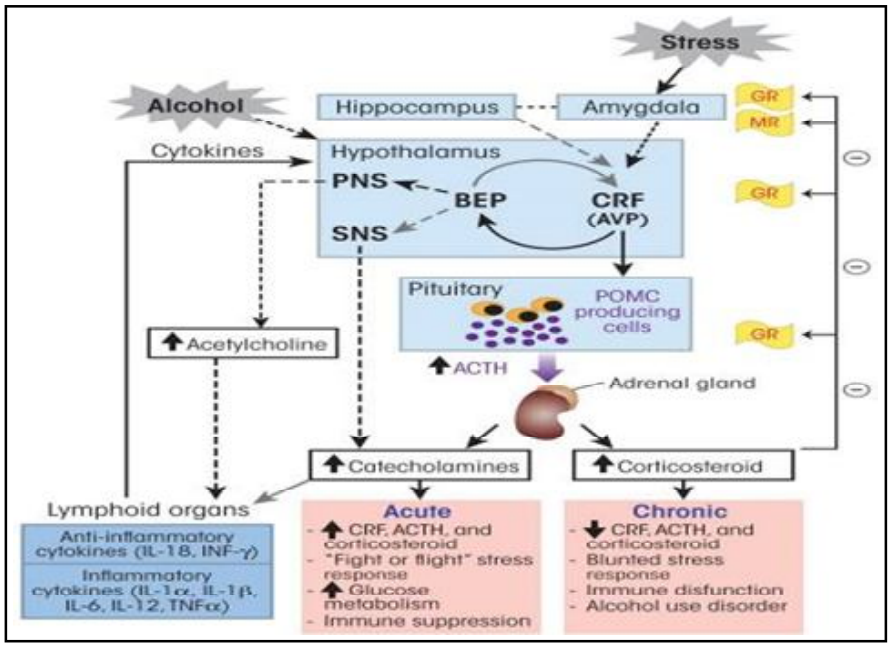

Fig. 1. Alcohol's effects on the hypothalamic–pituitary–adrenal (HPA) axis and the stress response (Sarkar et al., 2017)

then start a chain reaction of biological reactions to assist restore homeostasis. In their target cells, glucocorticoids bind to both low-affinity glucocorticoid receptors and widely dispersed high-affinity mineralocorticoid receptors to produce their effects. The expression of the genes that are responsive to glucocorticoids is then positively or negatively regulated by these receptors when they go to the cell nucleus and bind to specific DNA sequences known as glucocorticoid response elements (Sarkar et al., 2017).

The activity of the HPA axis is regulated through several feedback mechanisms. The principal protection against overactivation of the HPA axis involves the glucocorticoids (e.g., cortisol) through a negative feedback loop. Thus, glucocorticoids bind to mineralocorticoid (type 1) receptors and glucocorticoid (type 2) receptors in the hypothalamus, hippocampus, and pituitary. This binding decreases CRF, AVP, and ACTH production (Fig. 1). An additional negative feedback mechanism involves the BEP produced from POMC, which is synthesized in the ventromedial arcuate nucleus of the hypothalamus after stress activation. CRF release by cells from the PVN of the hypothalamus activates this BEP synthesis and release, which then inhibits further CRF release, creating a negative feedback cycle[37]. These feedback processes help to maintain the cortisol concentration within a narrow physiological window and switch off the stress response[32,50].

B. Effect on Human HPA Axis :

Heavy drinkers have greater amounts

of the hormone, indicating reduced control and chronic changes of the hypothalamic-pituitary-adrenal axis. Excess cortisol levels, a product of the hypothalamic-pituitary-adrenal (HPA) axis, have been shown to be detrimental to health[14]. One manifestation of alcohol's effect on the HPA axis[22,42] resembles a disorder called Cushing's syndrome, a disease stemming from an excess of cortisol[41]. Clinical signs of the syndrome include obesity of the torso (with purplish stretch marks); a round, red face; high blood pressure; muscle weakness; easy bruisability; acne; diabetes; osteoporosis; and a variety of psychological disturbances[5]. Women also may develop facial hair (*i.e.*, hirsutism) and menstrual disturbances[15]. Aside from drug-induced Cushing's syndrome, however, approximately two-thirds of cases of Cushing's syndrome are caused by ACTH-producing pituitary tumours[42]. Some cases of Cushing's syndrome are brought on by prolonged use of high-dose glucocorticoids as therapy for other medical conditions. Surgery to remove the tumours is the main form of treatment for the illness. Adrenal tumours account for 15% more Cushing's cases, while the remaining instances are typically brought on by tumours other than pituitary and adrenal glands that abnormally release ACTH and are typically found in the gut, lung, and pancreas. In order to treat these tumours, surgery or, in some situations, medication is used[4,15] (Fig. 2).

Some drinkers develop a condition-called alcohol-induced pseudo-Cushing's syndrome. It is indistinguishable from true Cushing's syndrome ,although it tends to be clinically more mild. Proof that the pseudo-Cushing's syndrome results from alcohol consumption and not from tumorous over production of ACTH or cortisol derives from the observation that its symptoms and signs disappear with abstinence from alcohol, usually within 2 to 4 months. The prevalence of this syndrome among alcoholics is unknown, but clinical experience indicates that most alcoholics do not have the full blown syndrome. Based on alcohol's ability to activate the HPA axis in animals[47], the existence of alcohol-induced pseudo-Cushing's syndrome should not be surprising. However, it is unclear whether the illness is caused by alcohol's effects on the brain or at the pituitary or adrenal levels. But the existence of alcohol-induced pseudo-Cushing's syndrome suggests that drinking alcohol somehow causes the HPA axis to become clinically important in humans. Thus, the report suggests alcohol consumption has adverse effects on the adrenal cortex and may cause Cushing syndrome, stress, and alter other important functions that are controlled by those adrenal hormones (Fig. 2).

Effect of alcohol on Hypothalamic-pituitary-Gonadal axis (HPG Axis) :

Alcohol abuse and alcoholism are associated with disorders of reproductive function in both men and women. The hypothalamic-pituitary-gonadal axis (HPG) and its hormones are essential for proper functioning of reproductive system. In alcohol abusers, the HPG dysfunction was shown to be associated with a decrease in libido, infertility and gonadal atrophy. Several studies have clearly documented that alcohol has deleterious effects on all three components of the HPG axis, the hypothalamus, pituitary, and gonads. We will review some of these studies on the acute and chronic effects of alcohol on male and female reproductive systems.

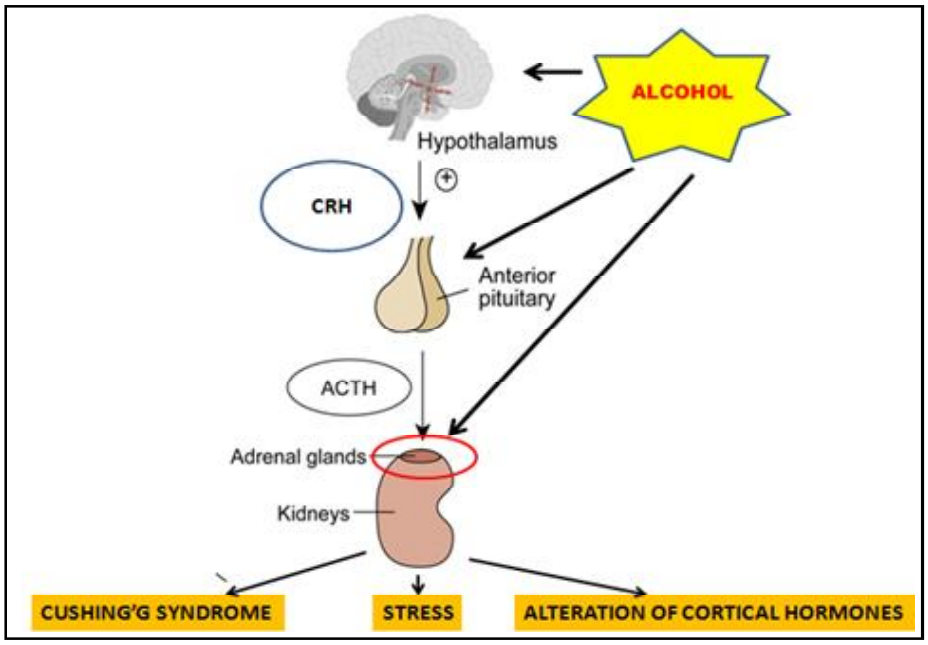

Fig. 2. Alcohol's impact on the hypothalamic-pituitary-adrenal axis and changes to cortical hormones.

Overview of male and female hypothalamic-pituitary-gonadal axis :

The hypothalamus in a pulsatile way produces and secretes the hormone called luteinizing hormone–releasing hormone (LHRH), also called gonadotropin-releasing hormone (GnRH), into the hypothalamic-pituitary portal network. At the anterior pituitary, LHRH binds to specific receptors on gonadotroph cells and stimulates a cascade of events that lead to production and secretion of two important gonadotropin hormones, follicle–stimulating hormone (FSH) and luteinizing hormone (LH) into the general circulation. In the ovary, during the follicular phase of each reproductive cycle (28 days in human cycle), FSH stimulates the development of a dominant follicle which, as it matures, produces and secretes increasing amounts of the estrogen called estradiol. Both FSH and LH stimulate estradiol secretion and this rise in estradiol is responsible for the LH and FSH surge seen in midcycle. LH then stimulates ovulation and the development of the corpus luteum during the luteal phase which then produces and secretes progesterone, an important hormone in the preparation of the uterine wall for the fertilized egg and for the maintenance of the pregnancy. In the testis, LH stimulates testosterone secretion while FSH controls the initiation and maintenance of spermatogenesis. In addition, testosterone, estrogen and progesterone, control their own production through a feedback loop mechanism and can act on the hypothalamus and the pituitary to either inhibit or stimulate the release of LHRH, LH and FSH [18,20].

Studies in men :

Diminished sexual function in alcoholic men has been clinically noted over many years; early studies largely attributed this problem to liver disease. However, when young, healthy, non-alcoholic volunteers were exposed acutely to alcohol, a fall in serum testosterone was consistently demonstrated.

Alcohol's effect in HPG Axis :

Numerous studies have documented alcohol's diverse deleterious effects on the HPG axis and its hormones. The resulting HPG dysfunction observed in people with AUD can be associated with diverse outcomes, including a decreased libido, infertility, and gonadal atrophy. It also is important to note that these deleterious effects are not limited to adult drinkers but may also affect adolescents in puberty who begin to consume alcohol. For more information, see the sidebar "Alcohol's Effects on the Hypothalamic–Pituitary–Gonadal Axis During Puberty" (Fig. 3).

The negative effects of alcohol on male reproductive function, including lower testosterone levels, have been extensively studied in both humans and animals (Fig. 3). Due to decreased hypothalamic LHRH release, acute alcohol consumption decreased the levels of LH and testosterone in the blood[11,12,44]. Contrarily, males with AUD had significantly lower levels of testosterone and progesterone compared to men without AUD, while chronic alcohol use dramatically elevated FSH, LH, and oestrogen levels[31]. According to Muthusami and Chinnaswamy[31], the AUD group also had considerably less semen volume, sperm count, motility, and morphologically normal sperm.

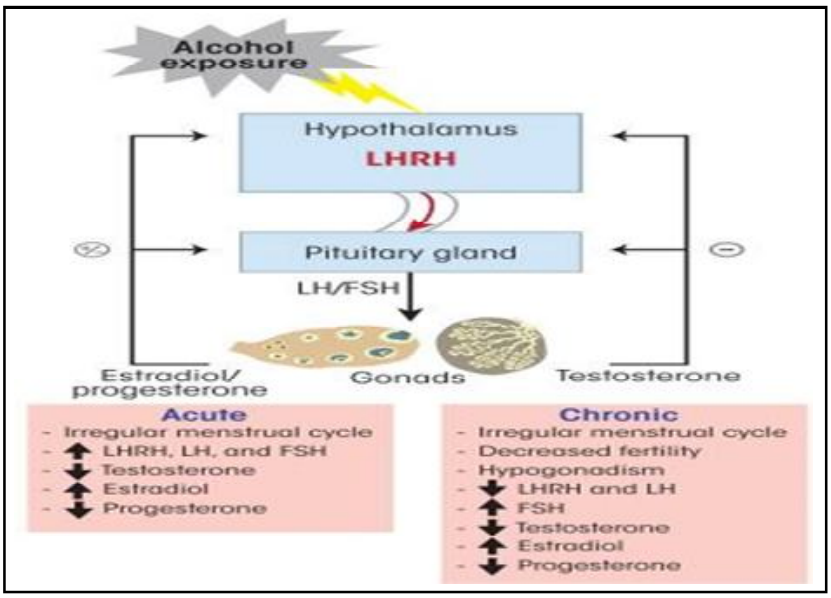

Fig. 3. Alcohol's effects on the hypothalamic–pituitary–gonadal (HPG) axis in male and female (Sarkar et al., 2017)

In male-

Ethanol increases the activity of the enzyme aromatase, which transforms androgens into oestrogens, particularly in the liver[38]. This mechanism might help to explain why excessive alcohol consumption causes hypogonadism even in the absence of liver damage.

IGF-1 can stimulate testosterone synthesis and spermatogenesis[43], so in men with cirrhosis and AUD, a decline in IGF-1 bioavailability as a result of liver disease may play a role in the development of hypogonadism[9] and elevated levels of estradiol and estrone in the blood[29]. Testicular cell damage may result from ROS generated during alcohol metabolism[16]. The testes of rats that were chronically exposed to ethanol were shown to have higher levels of the testicular alcohol-inducible cytochrome P450 2E1, which is involved in the production of ROS and hydroxyl ethyl free radicals[45]. By blocking protein kinase C, a crucial enzyme in the synthesis of testosterone, the alcohol metabolite acetaldehyde can interfere with the production of testosterone[10].

In female-

Women who drink alcohol are more likely to experience spontaneous abortions, irregular menstrual cycles, no ovulation (also known as an ovulation), early menopause, and other reproductive problems. Drinking alcohol—even as little as five drinks per week—was associated with lower fecundity[22] in healthy women between the ages of 20 and 35.

Thus, the report suggests alcohol consumption has adverse effects on the gonad and may cause alteration of reproductive hormone, infertility and alter other important functions that are controlled by those gonad hormones (Fig. 4).

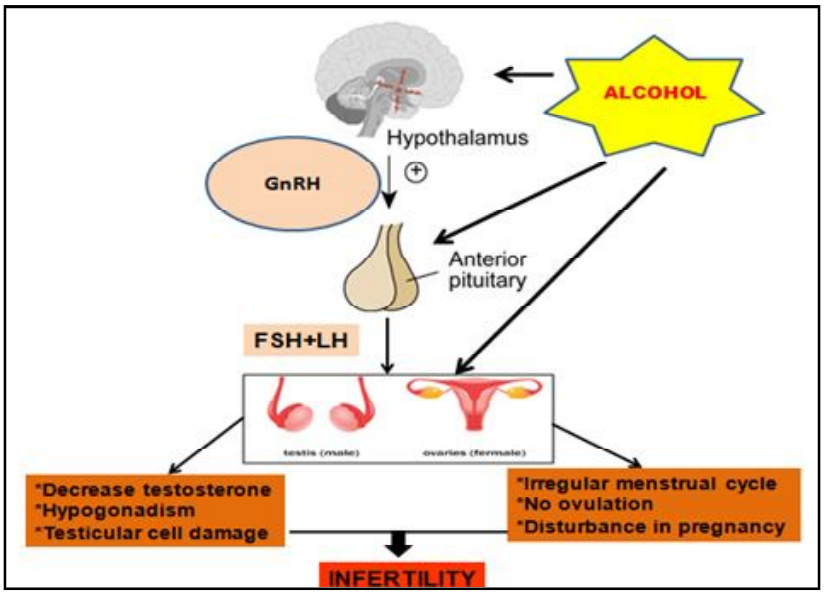

Fig. 4. Alcohol effects on gonads and causes infertility.

Effect of alcohol on pancreas :

The pancreas is one of the most important organs of the endocrine system that is involved in the tight control of blood glucose concentration through synthesis and secretion of a peptide hormone called insulin from ß-cells. Diabetes mellitus (DM) is a syndrome of dysregulated metabolism with high blood glucose levels (hyperglycemia) due either to an abnormal insulin secretion and/or signaling in peripheral tissues. DM is characterized by either a ß-cell deficit such as in insulin-dependent type 1 diabetes or reduced peripheral insulin sensitivity as in type 2 diabetes[20]. Type 2 diabetes is recognized clinically as a complication which often occurred in alcoholics. However, it was shown that the relationship between alcohol consumption and the risk of type 2 diabetes is a "U" shaped. Pancreatitis is a potentially fatal inflammation of the pancreas often associated with long-term alcohol consumption. Symptoms may result from blockage of small pancreatic ducts as well as from destruction of pancreatic tissue by digestive enzymes. In addition, by-products of alcohol metabolism within the pancreas may damage cell membranes[30]. Alcohol is thought to precipitate and make pancreatic secretions more viscous, which causes protein plugs to form in the small ducts and eventually form calculi. These calculi then cause progressive inflammation and fibrosis, which results in the loss of acinar, islet, and ductal cells[28,36]. Through increased peripheral insulin sensitivity, low or moderate alcohol use has been shown to reduce the risk of type 2 diabetes in some people[27]. Patients who drank moderate amounts of alcohol had a 30% lower chance of developing type 2 diabetes, whereas those who used 48 grammes or more of alcohol per day had no risk decrease at all. Whether moderate alcohol consumption affects insulin secretion is still very controversial. Some studies show that moderate alcohol consumption improves insulin action without affecting its secretion[1], whereas others show a reduced basal insulin secretion rate associated with a lower fasting plasma glucagon concentration[8]. Some studies also shown, in the same study, that the enhanced insulin sensitivity observed may be in part due to the inhibitory effect of alcohol on lipolysis. The beneficial metabolic effects of moderate alcohol consumption on insulin sensitivity and glucose tolerance may explain the significant reduction in the development of type 2 diabetes and the risk of cardiovascular disorders reported in several epidemiological studies[1,2]. Heavy alcohol consumption, on the other hand, is an independent risk factor for the development of Type 2 diabetes mellitus[48]. Heavy alcohol intake was thought to have detrimental effects on pancreatic ß-cell function in addition to its effects on peripheral tissues such adipose tissue and the liver, where it causes insulin resistance. In a study with 16 healthy volunteer non-drinkers and 10 chronic drinkers, it was discovered that the chronic drinkers' insulin response was lower than that of the control group[35]. Following oral or intravenous glucose loading in these two groups, they assessed the total integrated response (TIR) values for the hormones insulin and c-peptide. They discovered that the insulin and c-peptide TIR levels in the alcoholic group were both significantly lower than those in the control group. Moreover, the insulin TIR values after the oral glucose load were considerably greater in both groups than they were after the intravenous glucose

load, pointing to an incretin-stimulating influence on insulin secretion. Because the decrease was also seen when a glucose load was administered intravenously, these authors came to the conclusion that the lower insulin response seen in alcoholics was caused by ß-cell dysfunction rather of an enteroinsular axis failure. In another study by Kim and colleagues[25], it was shown that in mice exposed for 8 to 10 weeks to chronic alcohol, there was a significant increase in the impairment of fasting glucose and an increase in β-cell apoptosis, which were associated with a reduction in insulin secretion. These effects of chronic ethanol seemed to be mediated through a down-regulation and inactivation by tyrosine nitration of the enzyme glucokinase, a critical player in glucose metabolism that leads to an increased ATP production and therefore to insulin secretion by beta-cells. These effects were also associated with a decrease in Glut2 and insulin expression, which exacerbates alcohol action. In an in-vitro study on RINm5F β-cell line, it was suggested that ethanol generates reactive oxygen species (ROS) and induces β-cell apoptosis[13]. Long-term ethanol consumption induces FGF21 resistance-mediated pancreatic β-cell dysfunction, and thus diabetes pathogenesis risk[3]. All of these studies suggest that heavy alcohol consumption has deleterious effects on pancreatic β-cell function and on glucose homeostasis (Fig. 5).

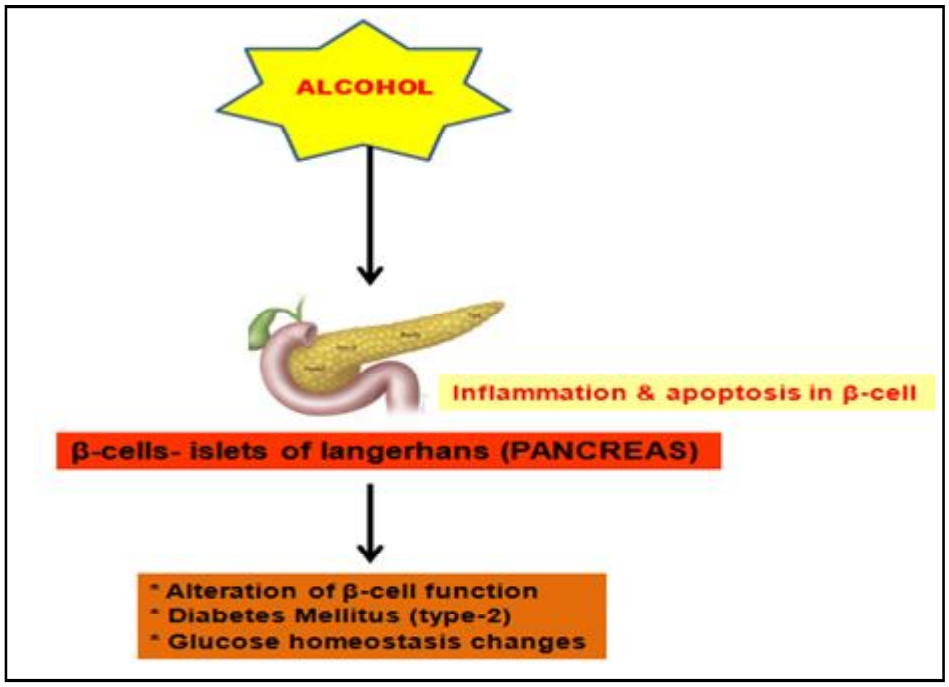

Fig. 5. Alcohol consumption affects glucose homeostasis and increases the risk of developing diabetes

Alcohol's effects on the hormonal (*i.e.*, endocrine) system have widespread consequences for virtually the entire body. Alcohol-related hormonal disturbances can result in cardiovascular abnormalities and reproductive deficits in both males and females. Other endocrine problems stemming from excess alcohol consumption include immune dysfunction and bone disease. Chronic consumption of a large amount of alcohol disrupts the communication between nervous, endocrine and immune system and causes hormonal disturbances that lead to profound and serious consequences at physiological and behavioural levels. Alcohol's deleterious effects on the endocrine system have far-reaching consequences that can result in serious physiological and behavioural disorders. Alcohol abuse not only causes hormonal disturbances, but because these disturbances permeate every organ and tissue in the body, can result in various debilitating disorders, such as stress intolerance, disturbed water balance and body osmolality, reproductive dysfunction, thyroid problems, immune abnormalities, diabetes, cardiovascular disease, cancer, and psychological and behavioural disorders. The different components of the endocrine system, particularly the HPA axis, HPG axis, normally communicate with each other as well as with the nervous and immune systems in response to external environmental cues and help maintain homeostasis and health. Researchers are exploring ways of using hormonal mechanisms to help treat alcoholics as well as to identify people predisposed to alcoholism.

Alcohol-related problems include immune dysfunction as a result of disturbances in cortisol, testosterone, thyroid hormones, insulin; reproductive problems; cardiovascular abnormalities stemming from disrupted glucose and lipid balance; and bone disease, among others. The World Health Organization, the European Union and other regional bodies, national governments and parliaments have formed alcohol policies in order to reduce the harm of alcoholism. Targeting adolescents and young adults is regarded as an important step to reduce the harm of alcohol abuse. Additional suggestions for limiting the harm caused by alcohol dependence and misuse include raising the age at which licit drugs of abuse like alcohol can be acquired and prohibiting or regulating alcohol advertising. It has been suggested to launch credible, fact-based media efforts to educate the public on the negative effects of alcohol abuse. Parents have also been given instructions on how to support children with mental health issues and prevent adolescent drinking.

References :

1. Avogaro, A., R.M. Watanabe. and A. Dall'Arche (2004). *Diabetes Care 27*(6): 1369–1374.
2. Bantle, A.E., W. Thomas. and J.P Bantle (2008). *Metabolism 57:* 241–245.
3. Bao, C.Y., Y.W. Shang. and L. Po Sing (2020). *Annals and translational medicine 8*(6): 310.
4. Barnes, P.J (2006). *British Journal of Pharmacology 148*(3): 245–254.
5. Bateman, A., A. Singh, T. Kral. and S. Solomon (1989). *Endocrinology Reviews. 10*(1): 92–112.
6. Berglund, M., and A. Ojehagen (1998). *Alcohol Clinical and Experimental Research 22* (7 Suppl): 333S-345S.
7. Bishehsari, F., E. Magno, G. Swanson, V.

Desai, R.M. Voigt , C.B. Forsyth. and A. Keshavarzian (2017). Alcohol and gut-derived inflammation. *Alcohol Research 38*(2): 163–171.

8. Bonnet, F., E. Disse and M. Laville (2012). *Diabetologia 55:* 3228–3237.
9. Castilla-Cortazar, I., J. Quiroga. and J. Prieto (2000). *Hepatology 31*(6): 1379.
10. Chiao, Y.B., and D.H. Van Thiel (1983). *Alcoholism: Clinical and Experimental Research 7* (2): 131–134.
11. Cicero, T.J., K.S. Newman and M. Gerrity (1982). *Life Sciences 31*(15): 1587–1596.
12. Dees, WL., N.H. Mc Arthur. and K.L. Farr (1983). *Biology of Reproduction 28* (5): 1066–1070.
13. Dembele, K., K.H. Nguyen. and T.A. Hernandez (2009). *Cell Biology and Toxicology 25*(2): 141–152.
14. Ellena, B., B. Martin, B. Annie, K. Clemens, M. Michael. and K. Meena (2008). *The journal clinical Endocrinology and Metabolism 93*(3): 750–757.
15. Emanuele, N. and M.A. Emanuele (1997). *Alcohol Health and Research World 21*(1): 53–64.
16. Emanuele, N.V, N. La Paglia. and J. Steiner (2001b). *Endocrine 14*(2): 213–219.
17. Friedman, H.S. (1984). *Alcohol 1:* 333–339.
18. Gardner and Shoback (2017). *Greenspan's Basic and Clinical Endocrinology* (10th ed.). McGraw Hill / Medical. pp. 49–68. ISBN 978-1259589287.
19. Geneva: World Health Organization (2018). Global status report on alcohol and health.
20. Guyton and Hall (2011). Text Book of Medical Physiology (12th edition). Saunders: Elsevier, pp. 907-937. ISBN: 978-0808924005.
21. Harrison, N.L., M.J. Skelly, E.K. Grosserode, D.C. Lowes, T. Zeric, S. Phister. and M.C. Salling (2017). *Neuropharmacology 122 :* 36–45.
22. Jenkins, J.S. and J. Connolly (1968). *British Medical Journal 2* (5608) : 804–805.
23. Jensen, T.K., N.H. Hjollund. and T.B. Henriksen (1998). *BMJ 317* (7157): 505–510.
24. Justyna, G., G. Francesca, C. Emanuele, M. Agnieszka, P. Nadia, Y. Tamara, Forbes-Hernández, L. Jose , B. Maurizio, V. Sandro La, M. Giuseppe. and G. Giuseppe (2022). *International Journal of Environmental Research and Public Health 19* (3): 1515.
25. Kim, J.Y., E.H. Song and H.J. Lee (2010). *Journal of Biological Chemistry 285* (48) : 37251–37262.
26. Koob, G.F. (2009). *Brain Research 1293:* 61–75.
27. Koppes, L.L., J.M. Dekker. and H.F. Hendriks (2005). *Diabetes Care 28:* 719–725.
28. Lankisch, P.G., M. Apte. and P.A. Banks (2015). *Lancet 386* (9988): 85-96.
29. Martinez, R.A., F.F. Santolaria. and R.E. Gonzalez (1995). *Alcohol 12*(6): 581–587.
30. Minoti, V.A., S.W. Jeremy. and A.K. Mark (1997). *Alcohol Health and Research World 21*(1): 13–20.
31. Muthusami, K.R. and P. Chinnaswamy (2005). *Fertility and Sterility 84* (4): 919–924.
32. Myers, B., J.M. McKlveen. and J.P. Herman (2012). *Cellular and Molecular Neurobiology 32*(5): 683–694.
33. Na, H.K. and J.Y. Lee (2017). *International Journal of Molecular Sciences*

18 (6): 1116.
34. O'Shea, R.S., S. Dasarathy. and A.J. McCullough (2010). *Hepatology 51:* 307–328.
35. Patto, R.J., E.K. Russo. and D.R. Borges (1993). *Mount Sinai Journal of Medicine 60* (4): 317–320.
36. Pham, A. and C. Forsmark (2018). *F1000 Research 7:* F1000 *Faculty Rev*-607.
37. Plotsky, P.M. (1991). *Journal of Neuro-endocrinology 3*(1): 1–9.
38. Purohit, V. (2000). *Alcohol 22*(3): 123–127.
39. Rachdaoui, N. and D. Sarkar (2014). *Endocrinology and Metabolism Clinics of North America 42*(3): 593–615.
40. Rachdaoui, N. and D. Sarkar (2017). *Alcohol Research 38*(2): 255–276.
41. Rasmussen, D.D., B.M. Boldt. and C.A. Bryant (2000). *Alcoholism: Clinical and Experimental Research 24* (12): 1836–1849.
42. Richardson, H.N., S.Y. Lee. and L.E. O'Dell (2008). *European Journal of Neuroscience 28*(8): 1641–1653.
43. Roser, J.F. (2008). *Animal Reproduction Science 107* (3–4): 179–196.
44. Rowe, P.H., P.A. Racey. and J.C. Shenton (1974). *Journal of Endocrinology 63*(2): 50P–51P.
45. Shayakhmetova, G.M., L.B. Bondarenko, V.M. Kovalenko. and V.V. Ruschak (2013). *Arhiv za Higijenu Rada i Toksikologiju 64* (2): 51–60.
46. Susanne, H.S. and A. Bartke (1998). *Alcohol Health And Research World 22* (3): 153–164.
47. Thiagarajan, A.B., I.N. Mefford. and R.L. Eskay (1989). *Neuroendocrinology 50* (4): 427-32.
48. Wei, M., L.W. Gibbons. and T.L. Mitchell (2000). *Diabetes Care 23:* 18–22.
49. White, A.M., M.E. Slater, G. Ng, R. Hingson. and R. Breslow (2018). *Alcohol Clinical and Experimental Research 42*(2): 352-9.
50. Wynne, O. and D.K. Sarkar (2013). Stress and neuroendocrine-immune interaction: A therapeutic role for β-endorphin. *The Wiley-Blackwell Handbook of Psycho-neuroimmunlogy.* Oxford: Wiley-Blackwell, pp. 198–211.