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Alcoholism And Bone Development: A Review

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ABSTRACT

Alcoholic preparations is one of the ingredients present in beverages, drugs or chemicals in common use even at pregnancy; and this is well acclaimed to be toxic to the conceptuses, particularly, the developing skeletal tissues.A thorough literature search at MEDLINE and consultation with local scientific publications, and text books on alcohol and bone development was carried out to compile useful information and to up-date knowledge on this subject. It is of great interest to note that this subject had been, and is yet receiving much and global attention from experimental, social and health workers; particularly echoing the hazards of alcohol abuse on developing tissues.This subject had been an area of much consideration, and yet calls for more attention with the view to unveiling the mystery of the toxicity of alcohol, while in search of therapy for its assaults and convincing means of abstinence for the addicts.

Keywords: Alcohol; Bone

The first empirical record of Sullivan (1899) on still-births and infant mortality rate of 56% compared to non-alcoholic users in Liverpool, England, which made this early worker conclude that "maternal intoxication" was the source of damage to the foetus triggered off interests in works on human fetuses following gestational ethanol exposure. This had earlier prompted the prohibition of (bridal) couples from drinking for fear of giving birth to defective children because according to Aristotle, 'foolish, drunken and harebrained women most often bring forth children like unto themselves: morose and languid'.

ETHANOL AS A FETO-TOXIN

The use of alcoholic beverages by pregnant women had long been shown to have far reaching consequences on the phenotype and behaviour of the offsprings; Jones and Smith (1973) named the pattern of craniofacial, limb as well as cardio-vascular anomalies and pre- and post-natal growth retardation assessed in a number of mothers as 'Foetal Alcohol Syndrome' (FAS). Consequent upon this observation by Jones and Smith (1973), experimental studies have shown that ethanol is teratogenic. Friedman (1985) found a case of babies with neural tube defects with a history of alcohol abuse during gestation. Various

Ethanol is of particular interest as a teratogenic agent because of its widespread use and numerous developmental defects in the offsprings exposed in utero (Adebisi 1995). Ethanol is the main ingredient in the three classes of alcoholic beverages: distilled spirit, wine and beer. Other forms of alcohol such as methanol have immediate toxic effects that make them unsuitable for drinking and, more so, they are easily metabolized in the body. Ethanol can be formed when fermentation is started in sugar containing plants by yeasts (Brengt 1990).

similar abnormalities have also been reported in animal studies, Chernoff (1975); Sulik et al., (1981); Ihemelandu (1984); Melvin (1985); Adebisi (1995; 2002a,b; 2003a, b, c, d). Growth impairment either antenatal, post natal or both is a feature of FAS and a common finding in Foetal Alcohol Effect (FAE). Severe growth retarded children do not show significant accelerated growth following rehabilitation. Few long-term follow-up studies done on children with FAS revealed that most of these children do not achieve normal adult stature, Streisguth et al., (1981).

ETHANOL DOSAGE AND FETO-TOXICITY

It is still debatable as to what amount of maternal alcohol consumption during pregnancy that can be regarded as safe for the foetuses. Opinions vary from those upholding the view that virtually any amount of alcohol ingested in pregnancy causes some intra-uterine developmental defects, Anonymous (1980; 1981) to those suggesting that only very heavy consumption has any effect, Mau, (1980). However, Pratt (1982) reported increased prevalence of congenital abnormality in infants of both moderate and heavy consuming pregnant women.

Some workers had suggested that if the teratogenicity of alcohol should depend on the dosage (of the consumed), this might then account for one of the reasons why offsprings of some alcoholic women show mild characteristic features of Fetal Alcohol Syndrome (FAS), which has been termed Fetal Alcohol Effect (FAE), Chernoff et al., (1975); Poskitt (1984). The phenotypic manifestation of ethanol induced anomalies in the offsprings of the users either as FAS or FAE is associated with the pattern of drinking, that is, either moderate or heavy.

Epidemiological studies have traced the choice for either heavy of moderate drinking to the following reasons among others: one, per capita income of individuals; two, the relative price and availability of alcoholic drinks, and three, family history of alcoholism, Anonymous (1980; 1981) although total abstinence from alcohol consumption has been attributed to religious, cultural or temperance reasons, Muller et al., (1986).

Growth impairment either antenatal, post natal or both is a feature of FAS and a common finding in FAE. Severe growth retarded children do not show significant accelerated growth following rehabilitation1 Adebisi (2002a,b). Few long-term follow-up studies done on children with FAS revealed that most of these **children do** not achieve normal adult stature, Streisguth et al., (1981). Common features of FAS include delayed ossification, retarded growth and fusion of epiphysis and diaphysis particularly of radius and ulnar, Spiegel et al., (1979); and in a study on babies born to mothers who received ethanol infusion during labor reported incidence of osteoporosis, achondroplasia and bone marrow anomalies were reported, Montoya and Lopez (1971). Moreover, in an experimental study on pregnant mice treated with ethanol, cases of axial skeletal dysmorphogenesis involving the fusion of vertebrae, absence of spine or arches, deformed ribs and sternabrae were observed, Padmanabhan (1985). Other reported observations include absence of skull vault, under-ossification and asymmetry of the constituent skull bones resulting in severe reduction of the cranial volume in rats, Adebisi (1995; 2002a,b).

On the other hand, examination of the feto-toxic effect of ethanol and maternal hyperthermia in the mice were conducted in which structural defects including skeletal and visceral malformations following combined treatment of a single dose of 25% ethanol and heat stress in a water bath at 42°C for 10 minutes on day 8 of gestation were reported, Shiola et al., (1988).

Also, in a study on the effects of gestational ethanol ingestion in non-human primates, thirtyone pregnant *macaca nemestria* were exposed to weekly ethanol doses ranging between 0.3 4.1g/kg maternal weight. Morphometric analysis performed on their cranial radiographs showed that animals exposed to high doses of ethanol had, on average, smaller, distorted crania than the control animals, Sheller et al., (1988).

It had recently been demonstrated that virtually any level of alcohol consumed produces a toxic response. Acute alcohol intoxication causes transitory hypocalciuria. Prolonged moderate drinking elevates serum parathyroid hormone levels while chronic alcoholics are characterized by low serum levels of vitamin D, with resultant malabsorption of calcium, thereby leading to hypocalcaemia and hypocalciuria, Laitinen and Valimaki (1991); Miralles-Flores and Delgado-Baeza (1992). The observation is more important in view of the fact that even in maternal alcoholism one does not find every alcoholic mother giving birth to a malformed child. It had been demonstrated that both acute and chronic alcoholism results to malabsorption of calcium, thereby leading to distortion in calcification, Laitinen and Valimaki (1991); Miralles-Flores and Delgado-Baeza (1992); Adebisi (1995).

GENETIC ROLE IN ETHANOL FETO-TOXICITY

The role of genetic factors in development is quite noteworthy. In simple terms the genetic make up of the developing organism is the setting in which induced teratogenesis occurs. Differences in the reaction to the same potentially harmful agent by

individual strains or species are presumed to depend on variation in their biochemical or morphological make up, which are in turn determined by the genes, Wilson and Fraser (1977). The facts that the mouse embryos are usually susceptible to cleft palate induction by glucocorticoids whereas most other mammalian embryos are resistant to this effect can be interpreted to mean that mice possess in-born chemical or anatomical features which make them more vulnerable (less resistant) to these agents than are other animals, and these are at least to some extent genetically determined. In another study conducted on fourteen pairs of identical twins born to heavily alcoholic women showed these children exhibiting FAS of deferring severity and in addition, significant differences in the individual rate of ethanol metabolism ranging from low value of 0.11mg/ml/hr to a high value of 0.24mg/ml/hr were also recorded. These reports are indicative of a possible dominance of the foetal genetic make up over that of the mother in determining the severity of the toxic or teratogenic effects of ethanol on the conceptuses in utero. To this end it has been suggested that the occurrence of anomaly is in part a measure of the inability of genetic and other regulatory mechanisms to overcome localized sensitivity of embryos to an external intrusion, Meredith (1964). This could be explained from the fact that chromosomal aberrations induced in somatic cells are the cause of malformation following exposure to teratogens.

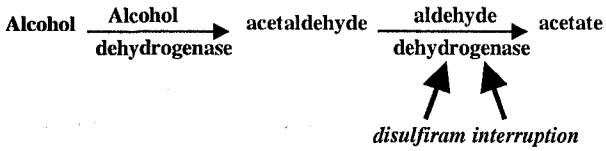
It is yet debatable whether the genetic component of the mother or that of the foetuses that is more important in determining the extent of the effect of a teratogen, since it has been observed that not all the offsprings of alcoholic women manifest the characteristic features of Foetal Alcohol Syndrome (FAS), Poskitt (1984) the rate of maternal alcohol metabolism could modify the effects of alcohol on the foetuses. Poskitt for instance reported a case of some non-drinking first degree relatives of alcoholics who were observed to show increased serum levels of acetaldehyde following one 'dose' of alcohol, suggesting that there may be genetically determined tendency to slow the metabolism of acetaldehyde in these individuals who if alcoholic may have infants with FAS. The possible suggestion that variations in genetic make-up and the associated differences in ethanol metabolizing capacities could be responsible for such differential responses had received wide support, Wilson and Fraser (1977); Poskitt (1984) and Chernoff (1975).

ETHANOL AND PLACENTAL PERMEABILITY

Ethanol is a molecule that easily moves through cell membranes. It is decreasingly absorbed from the proximal portion of the small intestine, the stomach, the large intestine, the buccal and oesophageal mucosa, and rapidly equilibrates between blood and tissues, Schapira, (1990). The placenta is given credit for serving as a barrier behind which the embryo or fetus is protected from foreign chemicals. Available evidence seems to indicate that virtually all unbound chemicals in maternal plasma have access to the conceptuses across the placenta, Wilson (1954). Many small molecules less than 600ml. wt., and low ionic charges cross by simple diffusion, others by facilitated diffusion, active transport, pinocytosis or perhaps also by leakage. Lipophilic chemicals are known to cross the placenta and other membranes more readily than other compounds Wilson (1977). It now seems that the rate, as determined by size, charge, lipid solubility, affinity to complex with other chemicals and so on also play a significant role in placental permeability. Ethanol with a molecular weight of 46.07 has been shown to pass freely across the placental barrier and that its concentration in the fetus is almost as high as in the mother, Jones (1973).

The total dose of a chemical reaching the conceptuses is a product of interaction of many variables, some relating to maternal, functional capacity, others dependent on the nature of the chemical itself and yet others undoubtedly reflecting the complex characteristics of the placenta, Wilson and Fraser (1977). The possible interruption of utero-placental blood flow by the chemical had also been suggested, Bengt (1990).

The use of ant-abuse such as disulfiram by pregnant alcoholic women could increase the severity of foetal deformities, Nora et al., (1977). Alcohol is predominantly metabolized in the liver. It involves two main routes, dehydration of alcohol in the cell cytosols and ethanol oxidation in the microsomes of the smooth endoplasmic reticulum, both result in the production of acetaldehyde, which is oxidized to acetate, Schapira (1990). Disulfiram interrupts the metabolism of ethanol as follows by intercepting aldehyde **dehydrogenase:**



This leads to increased level of blood acetaldehyde which may be more damaging to the foetuses than ethanol itself; acetaldehyde has been reported to depress oxygen uptake by the developing cells, Ob and Ristow (1990).

Unfortunately, certainty of the specific site of action of the teratogenic agents within the maternal-placenta-foetal unit is almost non-existent. All too frequently, the naïve assumption is made that the administered agent find its way to the foetus and directly interfere with the growth and differentiation of these cells. Not only is such evidence available but also larger numbers of clues actually indicates that these chemicals do not act directly on foetal cell. For instance, as early as 1971 it was pointed out that the concentration of the teratogens, cortisone was no longer higher at its site of teratogenicity in the foetus than it was in any other foetal tissues and its site of action, and that its concentration in all the tissues were lower than in the maternal tissues, Waddell and Marlowe (1976). Comparison of maternal foetal concentration ratios of variety of chemicals with low or high teratogenic potentials revealed that this tendency was considered: that is, the potent teratogens have high foetal maternal ratios according to Waddell and Marlowe (1976). However, this naïve assumption is untenable, that the greater the amount of chemical reaching the foetuses, the more likely the production of foetal anomalies, and the problem had now become a search for the sites within the entire maternal-placenta unit.

Lately, the predominant directions of reports are on the action that produces anomalies by their effects on the placenta. Direct effects of the agents on the mothers may be as frequent as those acting directly on the foetus. However, the total dose of a chemical reaching the conceptuses is a product of interaction of many variables, some relating to the maternal functional capacity, others undoubtedly reflecting the complex characteristics of the placenta. The possible interruption of utero-placenta blood flow by the chemical had also been suggested, Bengt (1990).

DEVELOPMENTAL ASPECTS OF BONE GROWTH

Bone is a vascularized, supporting skeletal tissue, although it may arise ectopically outside the skeleton; which is deposited by osteoclasts and oesteocytes, and hence, remodelled by osteoclasts. Glycos-amino-glycans and collagen of type I compose its extra cellular matrix, which is permeated by canals and impregnated with hydroxy-apatite, Hall (1988 - 1991). Bone function to support the body, act as a storehouse for calcium and phosphorus; and for haematopoietic activity in adults, and as major site of metabolic regulations of mineral homeostasis. Bone is found only in vertebrates and had been classified on the basis of developmental origin: as either endochondral, that is, developing by replacement of cartilaginous model; or intra-membranous, that is, developing by the replacement of fibrils or fibro-cellular model, Hall (1988-1991). The processes that produce each type of bone differ, but basically these follow the formation of primary osteon. The primary osteon has a central canal of diameter less than 100u and it lacks a cement line, while having two or more central vessels and is wedged between interstitial lamellae. The life span of osteons and the time required to produce them vary from one species to another. For instance in a 2 year old cat, it takes about 50 days while in a 45 year old man the process takes 100 days. The life span of an osteon is 15 years, thus only about 0.05% of the skeleton is turned over per day. The rate at which an osteon mineralises is rather not uniform. While 70% of the mineralisation occurs within one or two days of deposition of the non-calcified osteoid, the remainder can take many months. The term osteoid was used to describe the recently deposited, unmineralised, metabolically active bone found adjacent to either periosteal or endosteal bone surfaces; these are lined by the formative cells (osteocytes); the resorptive cell (oesteoclasts) and bone precursors cells, (oesteoblasts) lining the periosteal surfaces. Those on the endosteal surfaces are osteoclasts precursors. The bone surfaces are of primary importance in metabolic function, in reaction to vitamins and hormones and in the initiation of pathological changes. Moreover, these reports had led to the conclusion that there are separate precursors for osteoblasts and osteoclasts; while the osteoclasts can be readily distinguished from the multi-nucleated bone resorptive osteoclasts, their precursors cannot be distinguished readily from one another. However, osteoblasts had been found to originate from pre-osseous tissue, that is, hyper trophied chondroblasts being capable of transforming to osteoblasts, Thesingh

(1990), while the osteoclasts were shown to be of haematopoietic origin as they arise from hematogenic cells, Hageenars et al., (1989).

ETHANOL AND BONE GROWTH

Recent report that alcohol consumption inhibits bone growth and development in young actively growing rats came from a study in which 35%-ethanol-derived-calories was fed to 4- weeks- old female Sprague Dawley rats, and almost all morphological parameters of the bones were retarded as seen in bone density and peak bone mass, in both cortical and cancellous bone, Sampson et al., (1996). The authors concluded that the negative impact of alcohol on growing bone is not due to the secondary effects of altered bone mineral regulating hormones, because no significant differences in serum calcium levels, osteocalcin or growth hormones levels were found in their assessment.

Another related work had reported the assessment of bone mineral density of the lumbar spine and femoral neck in 25 women who were alcohol dependent, in which the mean bone mineral density was 6.8% lower than at the femoral neck and 6.9% lower than at the lumbar spine when compared with their 25 control subjects, Clark and Sowers (1990). Odvina et al., (1995) in a comparative assessment of the effect of moderate and heavy alcohol consumption on bone mineral density in black and white subjects, it was reported that the mean value for bone mass density of the lumbar spine, hip and femoral neck were not significantly different between alcoholic subjects and their respective controls among either blacks or whites, whereas, in white subjects, age and duration of alcohol were noted to have significant independent effects on the total body mineral density (BMD); and that prolonged heavy alcohol in take results in bone loss in white subjects, whereas, in blacks, age was the only factor that significantly affected bone mass independently and that the skeleton of black subjects may be less affected by alcohol. However, the explicit work had assessed BMD on categorised series of 458 alcoholic men as: low, medium and high alcohol intake (unit / week); these men recorded correspondingly BMD depending on the rate of alcohol consumed.

Further more, Feskanich et al., (1999) examined the risks and benefits of moderate alcohol consumption in 188 white postmenopausal women aged between 50 and 74 years revealed though chronic alcohol abuse is associated with low bone density and high risk of fracture, however, moderate alcohol consumption may help to maintain bone density by increasing endogenous estrogens or by promoting secretions of calcitonin. Women who consumed 75g or more of alcohol per week had significantly higher bone densities at the lumbar spine compared to non-drinking women. Other observations from the study include linear increase in spinal bone densities over increasing categories of alcohol intake, suggesting that alcohol intakes of less than 75g/week may also be of benefit. Also the femoral bone density did increase among drinkers with increasing level of alcohol consumption, Feskanich (1999). On the contrary however, it had been argued that moderate alcohol consumption does not augment bone density with a dosage equivalent of two glasses of wine per day usually consumed by women

The exact mechanism by which alcohol mediates its teratogenicity is still debatable. Opinions range from the reports that ethanol has a direct effect upon osteoblasts functions; and this had initiated the assessment of osteocalcin level, a vitamin-K dependent protein, which is synthesized by osteoblasts, since the rate of osteocalcin synthesis is thought to be a measure of osteoblast activity. The investigation reported decrease in osteocalcin levels, following ethanol treatment, suggesting a decreased osteoblast activity; this however, only correlates with liver function enzymes, ethanol dose, ash weight and bone strength, but not parathyroid hormone or cortisol, and this has been considered to be rather a direct consequence of ethanol intoxication on cells, Sampson et al., (1999).

In an earlier but inconclusive study, Farley et al., (1985), it was demonstrated that ethanol altered the reaction kinetics of the membrane bound alkaline phosphatase and membrane fluidity, as a means of potentiation of its toxic action. An old time suggestion that ethanol impairs DNA - synthesis and cellular proliferation directly by altering polyamine metabolism had received wild appraisal and the present research is in agreement with this view, Klein et al., (1996). Severe folic acid deficiency in the gestational ethanol exposed mice foetuses had also been indicated; and that acetaldehyde the main metabolite of ethanol induced both the depression of intestinal absorption of the vitamin from exogenous source and its supply from endogenous synthesis by bacteria Chernoff (1975); Hurley (1977). Folic acid is a known precursor in DNA and protein synthesis, and this was considerably impaired in folate deficient animals, as had been earlier observed Preedy et al., (1990); Friday and Howard

(1991). The impairment of protein (collagen) synthesis following alcohol induced folate deficiency could possibly explain the anomalies commonly seen in the investigation studies. The delay in calcification and retarded bone morphology and growth in the ethanol treated foetuses could be associated with the inhibitory effects of ethanol on nucleic acid and protein synthesis, and consequently poor matrix lay down at on set of osteogenesis, Chernoff (1985); Adebisi (1995). Anderson (1978) had indicated that within the new matrix were vesicles, that is, minute rounded structures that ranges from 30nm to 1um in size, present in osteoid tissues undergoing calcification. The vesicles provide pyro-phosphatase enzymes, which destroys inorganic inhibitors of calcification. Ethanol also probably has a fascilitatory effects on the action of the calcification inhibitors, that is, a family of inorganic pyro-phosphatases, phosphonates and di-phosphonates. They act normally to prevent calcium deposits from forming on soft tissues. Hence, the combine effects of the impairment of protein synthesis and cellular proliferations by alteration of polyamine and cellular proliferation by alteration of polyamine metabolism induced by folate deficiency, in addition to a direct inhibitory effect of ethanol on bone cell activities are accountable for the findings in such studies Friday and Howard (1991); Klein et al., (1996); Sampson et al., (1996; 1999). The effects of chronic consumption of ethanol on 10 months and 19 months old rats had also been investigated, and similar decrements in bone densities, mineralisation and all the morphological parameters considered were observed, Turner et al., (1991).

CONCLUSION

Generally, the effects of intra uterine exposure to ethanol appear to be persistent to adulthood. Compensatory or reversible growth is not fully achieved even in view of alleviating measures. The hypothesis that growth retardation of bone due to ethanol consumption is modified by impairment of folate uptake by the foetal tissues as previously tested, exhibited in the differential bone growth, morphology, mineralisation rate and birth defects is now well established; but the actual mechanisms of these actions are yet debatable and this had since stimulated unending interests and numerous researches particularly in the field of teratology. Although total abstinence from alcoholism doubtlessly would instil prevention of malformations in the conceptuses, therapeutic measures on the other hand would be helpful to the addicts. It now appears that the majority of cases of congenital malformations are associated with environmental factors. More so, this appears to be the category in which the most successful preventive measures could be instituted. It is for this reason that so much attention had been devoted to the study of exogenous factors or altered maternal environment of the foetus.

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