Mini review paper

Marijuana use and its effects on the kidney

Abstract: Cannabis (marijuana) continues to be the most commonly used illicit psychoactive substance globally. However little is known about trends of marijuana use in a large proportion of the world's population, including in India. Some countries such as the United States have legalised marijuana use in some states for recreational and medicinal uses. In animal models, the endogenous cannabinoid (eCB) system plays a role in regulating kidney hemodynamics and sodium transport and may contribute to the pathogenesis of diabetic and obesity-related nephropathy and kidney fibrosis. Although there is no evidence currently that marijuana use plays a role in the pathogenesis of kidney disease, data in humans are limited to case reports of AKI in the setting of synthetic cannabinoid use. The present review focuses on the role of the eCB system in normal kidney function and in various diseases.

Key Words: Cannabis, marijuana, diabetic nephropathy, hemodynamics, obesity

Cannabis (marijuana) continues to be the most commonly used illicit psychoactive substance globally. The National Survey of India (1) conducted in the year 2004 also reported that it is the most commonly used illicit substance in India too. However little is known about trends of marijuana use in a large proportion of the world's population, including in India. Some countries such as the United States have legalised marijuana use in some states for recreational and medicinal uses. Subsequently, it has been reported that marijuana use has increased over the last decade (2, 3,4).

Marijuana is derived from the Cannabis plant (hemp) of which the two main species include Cannabis sativa and Cannabis indica. The Sativa species contains strong fibre and is mainly used for industrial purposes (such as hempfibre), while indica variety has medicinal and recreational uses. It contains > 60 cannabinoid molecules including ▲9-tetrahydrocannabinol which is primarily responsible for its psychoactive properties. The discovery of this molecule led to the identification of the endogenous cannabinoid system and their ligands including those in the kidney. In animal models, the endogenous cannabinoid (eCB) system plays a role in regulating kidney hemodynamics and sodium transport and may contribute to the pathogenesis of diabetic and obesity-related nephropathy and kidney fibrosis. Although there is no evidence currently that marijuana use plays a role in the pathogenesis of kidney disease, data in humans are limited to case reports of AKI(Acute Kidney Injury) in the setting of synthetic cannabinoid use (5,6). The present review focuses on the role of the eCB system in normal kidney function and in various diseases.

The relevance of the endocannabinoid system: Marijuana has been found to have medicinal effects in addition to its recreational and psychoactive properties that have been recognised for centuries (7). In the last few decades, more so over the last decade or so, the discovery of cannabinoid molecules and their cannabinoid receptors in the brain and elsewhere have enhanced discoveries in the field of cannabinoid research. More than 60 plant-derived cannabinoid molecules have been identified in marijuana, amongst which ▲9

tetra-hydrocannabinol (THC) is mainly responsible for its psychoactive properties (8,9). After this initial discovery, it took more than two decades to identify the THC binding site in the brain. (10) which was later cloned as the cannabinoid -1 receptor(CB1receptor)(11). In addition to the brain type CB1 receptor, a second cannabinoid receptor was identified in lymphoid tissue named CB2 (12). Both CB1 and CB2 receptors share approximately half (44%) of sequence homology and are G-protein coupled receptors that mainly signal via G1/G0 protein, though they may also activate G- protein-independent signalling pathways. These receptors are also expressed in the brain, liver, skeleton, kidneys and other tissues (reviewed in detail in 13, 14). The discovery of specific receptors for plant-derived molecules in mammalian cells led to a search for specific endogenous cannabinoid ligands. Two endocannabinoids (eCBs) (shown in Fig 1) have been identified-the first is arachidonoyl ethanolamide(AEA, anandamide) and 2-arachodonoyl glycerol(2-AG) (15). Unlike classical neurotransmitters, ECBs are not sored in vesicles, though the mechanism contributing to their release is not clear. The CB1 and CB2 receptors , eCBs and enzymes involved in their biosynthesis , transport and degradation jointly make up the 'eCB system''

Role of the Renal Ecb system:

Several reports have identified the presence of the functional CB1 receptor in the entire kidney I humans as well as in rat and pig animal models. This includes the afferent and efferent arterioles , glomeruli , loop of Henle and collecting duct(14,15). It has also been expressed in podocytes and mesangial cells(17). Unlike CB1 receptors , there is still controversy regarding the expression of CB2 receptors in the kidney . Some reports have found abundant expression in human and rat podocytes, proximal tubule cells and mesangial cells(18). While the kidney cortex has similar levels of AEA and 2 A-G , the renal medulla has more than two-fold higher levels AEA than 2-AG (19).

Function of the Ecbs on renal function:

AEA has been found to cause vasodilatation of the juxtamedullary afferent arterioles via CB1 receptor and also stimulate the release of nitric oxide by renal endothelial cells , suggesting a key role of the eCB system regulating renal hemodynamics . Thereby renal blood flow increases leading to a fall in glomerular filtration rate(GFR). These effects can be completely blocked by CB1 receptor antagonists AM 281 and AM 251. AEA also (via CB1 receptor) stimulates the juxtamedullary production of NO around the loop of Henle, blocking the apical Na+/ H+ transporter and Na+/H+/2 Cl_ co-transport activity, creating a diuretic action(20).

Role of eCB in Diabetic Nephropathy (DN): The first direct role of the CB1 receptor involvement in DN comes from the clinically relevant animal model of DN produced by cisplatin (21). Increased levels of AEA but not 2AG were found. More direct contribution of the CB1 receptor to DN were found in murine models for Type -1 and Type-2 DM. In the first model induced by streptozotocin (STZ). Kidney expression of the CB1 receptor is enhanced in diabetic mice(22) and colonization of the CB1 receptor with nephrin points to their predominant expression in podocytes. Using a mouse model, it was shown by Hsu et al(23) that CB1 receptor activation/ stimulation increased urinary protein levels. The CB1 receptor has been found to be one of the mediators involved in mediating high glucose-induced podocyte dysfunction, modulation of tubular damage including apoptosis, activation of inflammatory pathways and causation of renal fibrosis. Unlike CB1, several lines of

evidence have shown that CB2 receptor has a protective role in the diabetic kidney. Downregulation of the CB2 receptor occurred following exposure to high glucose by reduction of mRNA levels. While CB2 receptor expression is unaffected in STZ –induced diabetic mice and rats (18) ,its glomerular expression is downregulated in patients with advanced DN. Chronic treatment of STZ-induced diabetic mice with the selective CB2 agonist AM 1241 ameliorated albuminuria and antagonistically CB2 receptor deletion in STZ –treated mice exacerbated albuminuria, renal function , nephrin and podocin loss and caused mesangial expansion(24).

ECBs and Kidney –dysfunction in obesity: Obese individuals have a three –fold greater risk of developing endstage renal disease (ESRD) than non –obese individuals(25). Even in the absence of DM and hypertension , which may be co-existing conditions in obese individuals ,obesity induces hemodynamic and morphological changes in the kidney,e.g glomerular hypertrophy, glomerular basement membrane thickening , mesangial matrix expansion and increased tubular inflammation. Recent evidence suggests that overstimulation of the eCB system via the CB1 receptor contributes to the pathogenesis of obesity and the metabolic syndrome. By activating CB1 receptors in the brain, eCBs produce marijuana-like effects including an increase in appetite and lipogenesis(26). CB1 receptor null mice are resistant to diet-induced obesity(D10) hepatic steatosis and associated hormonal and metabolic changes even though their calorie intake may be similar to wild type mice. The kidney being the major source of eCBs and contains the CB1 receptor, the possible role of the eCB system in regulating obesity-related kidney dysfunction has to be explored further.

Relevance of Cannabis use in India :

Cannabis has been reported to be a commonly used psychoactive substance among treatment seekers in various Indian studies (27). Venkatesan et al observed changing characteristics among treatment –seeking substance users across three decades(1985-2006) and reported cannabis use in 28% of the polysubstance users ,second only to alcohol(27). Long term trends in cannabis use have been studied in other countries as well. National prevalence of daily cannabis users among the general population in Australia fluctuated between 14.9% and 16.4% over the previous decade(28). The 2011 annual report from European Monitoring Center for Drugs and Drug Addiction (EMCDDA) reported the age group of 15-24 years to have the lifetime prevalence of cannabis use (30%) in Europe (29). Recent worldwide trends indicate rising prevalence rates of cannabis use and cannabis-related hospitalization with adolescents and young adults being especially vulnerable. It is in this context that the long term side effects including those on the kidney of marijuana use need to be seen.

Role of cannabinoids and their therapeutic use in symptom management in chronic kidney disease:

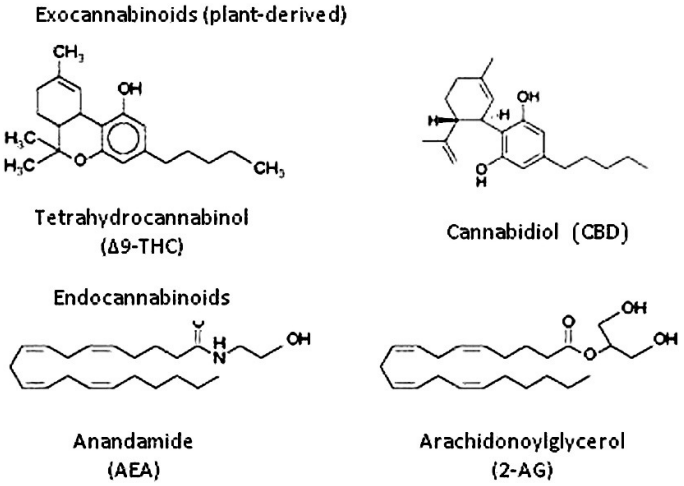
Pain is one of the most commonly experienced and debilitating symptom of patients with CKD. Approximately 50% of dialysis patients and those with advanced CKD who choose to be managed conservatively experience chronic pain with 82% reporting this pain as moderate to severe in intensity (30,31). Pain is experienced in the context of numerous other physical and emotional symptoms, all of which impact HRQOL negatively. The overall symptom burden of patients with advanced CKD is similar to that of many cancer patients in palliative care. Till now NSAIDS and opioids have remained the treatment of choice for these patients. Despite pain relief, opioid adverse effects may lead to adverse side effects and add

to the symptom burden. The rationale of considering cannabis-based medication is based on the encouraging results of CB agonists in the treatment of not only intractable pain but also in the treatment of other symptoms problematic in CKD such as nausea, anorexia, pruritus, anxiety and an overall lack of well being. A systematic meta-analysis of seven double-blind, placebo-controlled trails of CB-based treatments for multiple sclerosis-related neuropathic pain demonstrated the efficacy of cannabis therapy in controlling pain when compared to placebo(32). A more recent randomised placebo-controlled study of CBs as adjunctive treatment for refractory cancer-related pain in 177 patients (33). CBs are thought to act centrally through activation of the CB1 receptor to inhibit emesis. There is a growing body of evidence that cannabis-based medicine may be beneficial for many of the symptoms experienced by CKD patients, some of which opioids can exacerbate.

CBs are metabolised rapidly in the liver by the cytochrome P450 enzyme system. Although the risk of clinically significant reactions is thought to be low, there remains the possibility of potential drug interactions with other medications and immunosuppressive agents given the polypharmacy in patients with CKD. All CBs have a large volume of distribution and are highly lipid soluble and protein bound with high tendency to accumulate in fatty tissue. They are unlikely to be removed effectively by hemodialysis. Although there are no data for oral cannabis-based medicine in CKD , tolerability and safety data in other patient population with chronic illnesses such as rheumatoid arthritis, multiple sclerosis and cancer are encouraging and show that cannabis-based therapy may be tolerated than conventional therapies for many symptoms. Dizziness appeared to be the most common symptom, ranging in prevalence from 9 to 59%(33).There is no current evidence to suggest tolerance to therapeutic effects , unlike in chronic opioid use.

Conclusions: The eCB system is present in the kidney where it is involved in various renal functions with important therapeutic implications. eCBs acting via CB1 receptor in podocytes, proximal tubule cells and mesangial cells have emerged as mediators of both diabetic nephropathy and obesity-associated renal dysfunction. We are only just beginning to realise the therapeutic potential of CBs in an alleviation of symptoms in CKD. The paucity of long-term efficacy data does not allow for the routine use of CBs in the management of symptom burden in CKD. However, they may present a reasonable alternative to pain and symptom management. The legal issues around their use and potential misuse need to be addressed before marijuana can be routinely prescribed medically in CKD .

Fig 1: Cannabinoid structure



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