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Review Article

KISSPEPTIN - NATURALLY OCCURRING HORMONE FOR NAFLD

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Abstract:

NAFLD (Non-Alcoholic Fatty Liver Disease) is the accumulation of excess fat in the liver. It is associated with metabolic disorders such as hyperlipidaemia, obesity, hypertension, and Diabetes Mellitus. Kisspeptin (KP) is a naturally occurring hormone in the human body produced from the kisspeptin neurons of the hypothalamus. It is encoded by a gene KISS1 and acts on the KISS 1R receptor. The name originates from the iconic chocolate "HERSHEY'S KISSESS, Pennsylvania". It has shown promising results in the treatment of NAFLD and progression to NASH (Non-Alcoholic Steatohepatitis), Cirrhosis and HCC (Hepato Cellular Carcinoma). High fat diet (HFD) fed mice/western diet i.e., NAFLD induced mice are treated with Kisspeptin which showed no fatty liver. When KISS1R receptor is deleted from the liver cells of NAFLD induced mice it developed fatty liver even though they are treated with KP's. In patients diagnosed with NAFLD and NASH there is increased level of Kisspeptin as a part of body's physiological mechanism. Additionally, it has many advantages on different organs. No side effects were seen with Kisspeptins in all the indications.

Keywords: Kisspeptins, NAFLD, Steatosis, Cirrhosis, Carcinoma, NASH, Hershey's Kissess.

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INTRODUCTION:

Non-alcoholic fatty liver disease (NAFLD) is accumulation of excess fat in the liver or hepatocytes who drinks too little or no alcohol¹. The liver damage caused by chronic alcoholism /habitual drinkers is different from NAFLD. It is coded by K76.0 according to ICD10 guidelines (w.e.f October 1st 2021)².

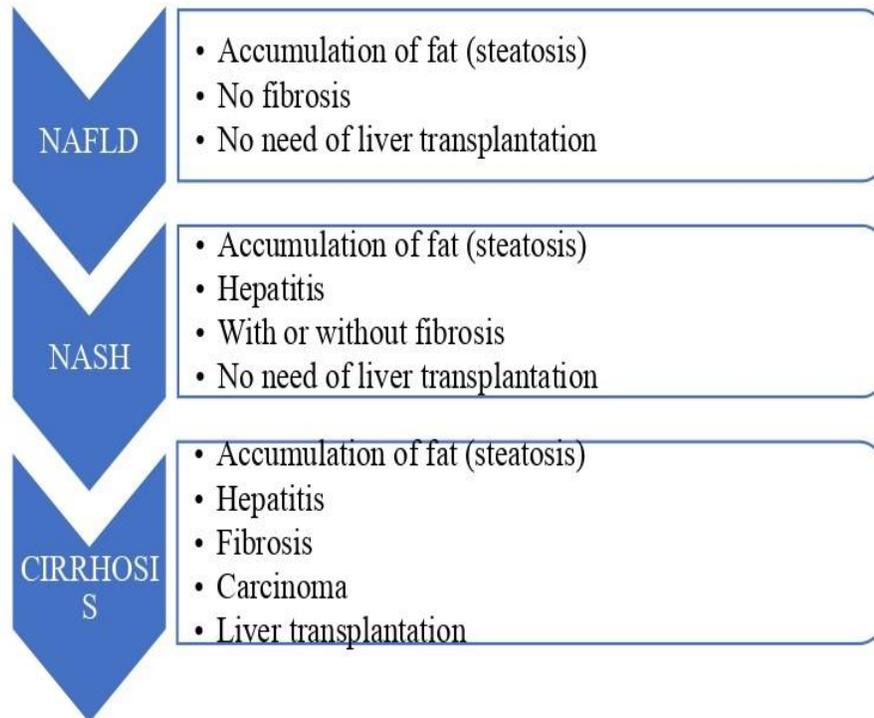


Table 1: Stages and Progression of NAFLD to cirrhosis^{7,8}

Causes and risk factors of the disease include metabolic syndromes like Diabetes Mellitus (insulin resistance), Hypertension, Obesity, hyperlipidaemia. About 9-32% of Indian population are affected with the disease annually³. It is called silent disease/killer as it develops no symptoms or very few symptoms like discomfort in right upper abdomen, fatigue, sudden weight loss⁴. Blood tests, Liver function test's (LFT's), lipid profile, bio markers (ALT, AST,

GGT, ALP), biopsy are used in diagnosing NAFLD and differentiating it from NASH. There is no current approved treatment for the disease but symptomatic treatment is relieving the condition (Vitamin E, Metformin, Pioglitazone)⁵.

Recently, a naturally hormone KISSPEPTIN showed promising results in NAFLD.

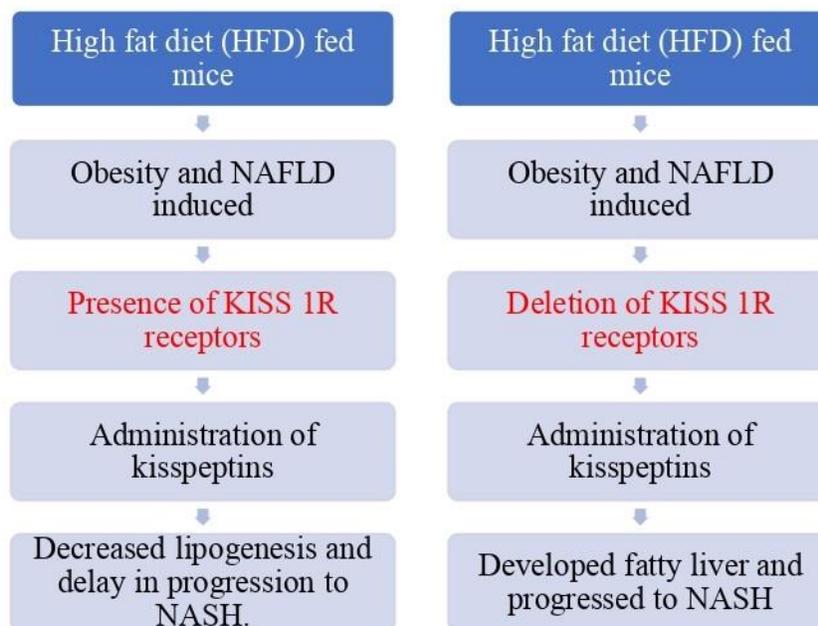
Kisspeptin, also called Metastatin-1 is a naturally occurring hormone produced from kisspeptin neurones of hypothalamus. The name Metastatin originates from the role of suppressing the metastasis in tumours like breast cancer. It is encoded by a gene KISS1 and acts on the KISS1R receptor. The name originates from the iconic chocolate "**HERSHEY'S KISSESS, Pennsylvania**"⁶. Along with K-Kisspeptin, N-Neurokinin B and D-Dynorphins are released from these neurones, so they are collectively called 'KNDy's' Or pronounced as 'CANDY'.

Figure 1: Chemical Structure of Kisspeptin^{14,15}**Kisspeptin role in NAFLD:**

It acts on its receptor KISS 1R and activates an energy regulator AMPK (5'- Adenosine monophosphate activated protein kinase). This results in decrease of lipogenesis and delays the progression of NAFLD to NASH.

Rutgers researchers and Imperial College, London

have worked collaboratively for a span of 15 years on effect of kisspeptin in liver diseases and concluded that it is having positive response in NAFLD by slowing its progression. The High fat diet fed mice/western diet fed mice i.e, Obesity and NAFLD induced mice were taken into the study and treated with kisspeptins. The mice did not develop fatty liver, fibrosis and NASH.

Table 2: Progression of NAFLD in the presence and absence of KISS 1R receptors^{7,8}

When the same study was repeated with the deletion of KISS 1R, the mice developed fatty liver even with the administration of kisspeptins. This concluded that kisspeptin is having a major role in NAFLD.

Human studies: In patients diagnosed with NAFLD, kisspeptin levels were noticed high compared with normal individuals as a part of body's physiological mechanism. Human trials are going on to study the effect of kisspeptin in different stages of NASH^{7,8}.

Other uses of kisspeptin:

β -cells of islet of Langerhans are encoded with KISS1 gene whose secretions are regulated by G protein-coupled receptors (GPCRs). In an incubated isolated mouse islet, insulin secretion was inhibited with 60 minutes exposure to kisspeptins (KP13 and KP54) at dose ranging from 10 nM, 100 nM and 1 μ M.⁹

The distribution of Kisspeptins and Kiss1r gene in hippocampus, posterior hypothalamus, medial preoptic area, medial septum and cerebellum of mouse brain regulates the food intake nuclei like Arc and PVN resulting in the changes of energy homeostasis and food intake.¹⁰

Kisspeptin-10 had increased the Respiratory quotient (RQ) but intake of food, size of meal, rate of eating & total energy expenditure (TEE) was decreased altering the metabolism and energy homeostasis. These changes were related with a rise in insulin, leptin, resistin, and High-Density Lipoproteins.¹¹

Gonadotrophins are crucial for the onset of puberty, for the regulation of sex steroid-mediated feedback and for the control of adult fertility. Such gonadotrophins secretions are controlled by Kisspeptin and secreted with the stimulatory effect of Kisspeptin on neurokinin B and dynorphin (KNDy neuropeptides). In humans when Kisspeptin is administered it resulted in the raise of LH secretion and LH pulse frequency.¹²

In the reproductive age women one of the most common reason for period loss is due to the decrease of LH pulsatility. This condition is referred as Hypothalamic amenorrhea

(HA). Kisspeptin activates the GnRH cascade and regains the GnRH/LH pulsatility in women.¹³

CONCLUSION:

From the pre-clinical studies done on mice models,

kisspeptin has shown slow progression of NAFLD to NASH. It also has other positive effects on other systems/organs and as it is a naturally occurring hormone it doesn't possess any side effects. Subjects who were already diagnosed with NAFLD has shown high levels of kisspeptin, so further clinical trails on the hormone are being conducted.

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