

Review Article

## Role of Sugar in Gall Bladder Carcinoma- A Review

Anindita Deb Pal

Assistant Professor, Department of Food Science and Nutrition Management, J. D. Birla Institute, Kolkata, India

### ABSTRACT

Sugar, the known poison has long been associated with the etiology of several chronic diseases including coronary disorders, metabolic diseases as well as cancer. Excessive consumption of the above interferes with normal cell signaling and metabolism thereby leading to development of physiological and metabolic stress. The present article highlights the involvement of sugar in the development and progression of gall bladder carcinoma. Gall bladder tumors rank fifth amongst the cancers of the liver and biliary tract. This type of cancer is generally associated with late diagnosis, poor prognosis and the paucity of targeted treatment options. Imbalanced intake of sugar rich food and beverages induces hyperinsulinemia, insulin resistance and diabetes mediated predisposition towards gall bladder carcinoma. Their consumption also elevates the chances of abnormal BMI, obesity as well as development of gall stones; all of which play a pivotal role in the manifestation of the above. These factors ultimately lead to the activation and upregulation of Insulin Dependent Growth Factor I (IGF) and its receptor (IGFR-1) which ultimately promotes tumorigenesis through modulation of cell growth, differentiation and inflammatory pathways. Therefore regular consumption of a balanced diet and maintenance of a healthy lifestyle may aid in prevention of numerous ailments including gall bladder cancer. Moreover, dietary interventions may also add on to the existing avenues of cancer prevention and therapy.

**Keywords:** Diabetes, gall bladder cancer, gall stones, IGF, insulin, obesity, sugar,

### INTRODUCTION

Cancer is a manifestation of uncontrolled cell differentiation and proliferation that ultimately accounts for an expansion of clonal population of cells leading to a tumor. Several factors including genetic, environmental, microbial, occupational as well as dietary have been associated with the initiation and progression of this disease. <sup>[1-2]</sup> Cancers of the gallbladder are one of the significant malignancies associated with the gastrointestinal tract and accounts for 80-95% biliary tract cancer cases worldwide. <sup>[3]</sup> It also ranks fifth amongst cancers of the hepato-biliary region. Gallbladder cancer is more prevalent in females compared to males especially in Asia and is generally documented to have a poor survival. <sup>[4]</sup>

Highest incidences of the disease have been reported in Pakistan, Chile, United States of America, Japan, Korea and Europe. <sup>[5]</sup> An increased incidence of this type of cancer has also been reported in India with the highest incidences observed in Northern India compared to the other parts of the country. <sup>[6]</sup> Unfortunately, most of the cases are detected at a later stage with poor prognosis, probably due to the silent progression of the disease and non specific manifestations of the symptoms. Late detection and undesirable prognosis may also be due to deficiency of characterized indications in the initial stages. Only a minor percentage of these cancers are detected in the early stages particularly during gall bladder cholecystectomy. The disease generally shows a survival of less

than five years post detection. Gall bladder diseases, inflammation, chemical exposure, microbial infection and dietary pattern have all been shown to predispose towards the above. Moreover, the scarcity of targeted treatment options available also contributes to the unfavorable prognosis of the same. [7] The disease has been observed to involve a complex cascade of cell signaling and growth pathways with the average five year survival rate being approximately 5%.

Sugar, a common dietary ingredient has often been associated with negative health consequences including diabetes, obesity, heart diseases and cancer. Elevated serum glucose levels have been associated with cancers of the stomach, esophagus, pancreas, liver, kidney, bladder, breast, lungs, cervix as well as leukemia. [8-10] Interestingly, gall bladder cancers have been shown to have a strong correlation with excess intake of energy and carbohydrate especially in the form of dietary sugars. [11] Elevated blood glucose levels have been correlated with increased chances of cancer mediated mortality. [12] Previous studies have indeed shown that increased consumption of dietary sugar elevates the risk of gall bladder cancer. Generally, commercial soft drinks have been found to contain 55- 130g of sugar per litre. Consumption of sugary beverages has been associated with weight gain, metabolic diseases and biliary tract cancer especially cancers of gall bladder. Sugary beverages increase the total energy and carbohydrate load in the body which further facilitates development of metabolic disorders and malignancy. Although the above effects may also be manifested by intake natural fruit juices, but their intensity is low compared to sucrose and glucose enriched drinks. Additionally, natural fruit juices are loaded with antioxidants, minerals, phytochemicals and fibers which display a protective role against tumors compared to sweetened soft drink. However, higher levels of even these juices may countermand the protective role of the above and ultimately add to the sugar

content of the body thereby aiding in development of cancer. Moreover, gall bladder cancers have mostly been positively correlated with beverages artificially sweetened with sucrose and glucose rather than natural fruit beverages. [13] In contrast to no consumption, intake of more than two servings of sucrose rich beverages has been observed to increase the risk of gall bladder cancer by at least two folds in both men and women. [11] Additionally, uptake of a balanced diet, high in whole grains, fruits, vegetables and low in refined sugar has been observed to significantly decrease the risk of chronic disorders including diabetes and cancer. [14] Dietary patterns play an important role in maintenance of a healthy lifestyle. Irregular consumption of meals prolongs the contact time of bile with the gall bladder accelerating the chances of development of gall bladder cancer. Previous studies have also associated poor sanitation and hygiene with an increased risk of the above. Although incidences of gall bladder carcinoma are observed worldwide, yet there is a huge ecological variation. [5] It has been hypothesized that changes in dietary lifestyle in different regions may account for this variation. [15] A strong correlation has been observed between dietary composition and gall bladder cancer. Sugars and carbohydrates have been attributed towards development of the disease such as diabetes, obesity and cancer while fruits and vegetables have a negative impact towards the same.

#### **Sugar mediated risk of gall bladder cancer is insulin dependent**

Regular intake of sweetened beverages is on a rise in recent times accounting for an increased energy intake of approximately 74kcal/day. Extended consumption of caloric food and beverages increases the concentration of blood glucose which thereby leads to hyperglycemia effecting the regulation of carbohydrate metabolism. Elevated concentration of glucose in blood stimulates increased insulin demand

culminating to heightened insulin levels. [16-17] Primary insulinemia that results because of increased insulin further has been shown to be responsible for sugar induced insulin resistance. It has been documented that under these circumstances, a condition known as compensatory hyperinsulinemia is also manifested as the body's attempt to relieve the temporary glucose spike. Increased demands of insulin progressively leads to  $\beta$  cell failure, further aggravating the glucose levels in blood. [18] Furthermore, increased glucose levels in the blood may also promote glucose toxicity induced oxidative stress mediated damage to the pancreas. Excessive levels of insulin leads to a condition of insulin resistance through their influence on glucose concentration, free fatty acids and hormone levels. Insulin resistance makes the utilization of increased loads of carbohydrates extremely difficult compared to normal insulin sensitivity thus potentiating the development of diabetes. These conditions have further been researched to accelerate glucose intolerance and diabetes. [19] In contrast to non-diabetics, diabetic patients have been shown to exhibit an increased risk of gall bladder cancer. [20] Hyperinsulinemia has been shown to increase the expression of insulin like growth factor receptor (IGFR-1) which results in development of malignancy in the gall bladder due to its ability to promote unregulated cell multiplication by increasing the progression of cells to the S phase of the cell cycle. [8] Aggressive tumors of the gall bladder have been identified with an over expression of IGFR-1 which also serves as a biomarker for this disease. [21] Results from previous clinical trials using antibody mediated therapy against IGFR-1 have proved its critical involvement in the disease. IGFR-1 is a cell membrane receptor involved in proliferation, differentiation and apoptosis. Increased expression and activation of this receptor modulates cell motility, adhesion, neo-angiogenesis and growth through the

phosphoinositide 3 kinase (PI3K) and Mitogen Activated Protein (MAP) kinase pathways. [22] Moreover, overexpression of IGFR-1 is often associated with poor prognosis of the disease. Furthermore, concurrent enhancement of glucose and liver dysfunction has been found to increase the risk of gall bladder tumorigenesis.

Consumption of sweetened beverages is a very common trend in modern times and regular consumers of these tend to have a less healthy dietary pattern compared to non consumers. It is a one of the major sources of additional sugars in the diet. Intake of sugar drinks have been related to high dietary sugar and energy. [11] Interestingly, sucrose, fructose or glucose sweetened beverages have also been shown to induce insulin dependent gall bladder cancer. [23] These glycosides have been observed to induce over expression of insulin and insulin like growth factor receptor (IGFR-1) receptor which thereby promotes excessive cell proliferation leading to the tumor. Insulin-like Growth Factor (IGF-1) reduces the synthesis of IGF-1 binding proteins thereby increasing the bioavailability of IGF-1 which has been documented to promote tumorigenesis by elevating cell multiplication and inhibition of apoptosis. [24] Utilization of these beverages including soft drinks, carbonated drinks and syrups has also been linked to increase in body weight and chances of diabetes mellitus, all of which predispose a person towards gallstone disease dependent cancer. [25-26] Glycemic carbohydrates have been positively correlated to increased chances of development of coronary heart disease, obesity, type 2 diabetes and tumors. Furthermore, elevated dietary Glycemic Index (GI) and Glycemic Load (GL) has been positively correlated with an increased risk of development and advancement of chronic diseases. However, this effect has been observed to be more prominent in case of high GI food compared to high GL foods. [27] Intake of a carbohydrate rich diet

consisting of low GI sources may be helpful in preventing chronic diseases as well as fulfilling the body's energy requirement. Additionally, decreasing the consumption of refined sugars reduces the development of metabolic disorders including diabetes which further decreases the chances of gall bladder carcinoma. Interestingly, dietary interventions have been proved to be an effective strategy to reduce the incidence of diabetes mellitus. Moreover, preventing the rate of carbohydrate absorption has been shown to reduce the possibility of transformation of altered glucose tolerance towards diabetes. The effects of glucose towards the risk of incident and fatal cancers of the gall bladder has been substantiated with evidences from studies conducted on cohorts from Korea, Europe, Australia, America and Asia. Consumption of sweetened soft drinks has been proved to dramatically increase the glucose and insulin levels in the body thereby increasing the risk of chronic diseases. [13] Moreover, the effect is more pronounced in individual with higher BMI. On the other hand, drinks containing natural and fermentable sugars have been observed to have a comparatively decreased influence on carbohydrate metabolic pathways. Increment of glycemic levels by every 1 mmol/l above the normal levels has been linearly associated with cancers of the gall bladder with the effect being more pronounced in women compared to men. [25] Excessive consumption of sugars only contributes to an increased GL as well as GI without providing any cancer protective benefits. Sugar also influence lipoprotein metabolism thereby leading to abnormal bile composition. Over consumption of sweetened drinks has indeed been portrayed to increase serum glucose levels as well as activate the pro-inflammatory pathways thereby leading to a condition of physiological and metabolic stress in the body. Consumption of sucrose sweetened food and drinks including cookies, sweet buns and soft drinks have been previously

associated with hyper insulinemia and diabetes dependent malignancy. Fructose and sucrose have been documented to activate the NFκβ inflammatory pathway and increase the levels of C reactive Protein (CRP). [22] Hence, excessive consumption of sugar sweetened commodities may predispose an individual towards insulin dependent gall bladder cancer.

### **Sugar increases the risk of obesity dependent gall bladder cancer**

Abnormal Body Mass Index (BMI) and obesity are also known as contributing factors towards gall bladder cancer. A BMI  $\geq 25\text{kg/m}^2$  has been associated with a heightened risk of gall bladder tumors. [24] They are a manifestation of an accumulation of energy due an imbalance between its consumption and expenditure. Moreover, increased glucose also induces the above thereby together contributing to the risk of carcinogenesis. Patients diagnosed as overweight and having an impaired glucose metabolism are indeed categorized to be prone towards gall bladder tumors. [28] Elevated levels of dietary carbohydrates induces the syntheses of Low Density Lipoprotein (LDL) cholesterol and reduces plasma High Density Lipoprotein (HDL) cholesterol which further induces altered BMI and risk of gall stones. [29] Previous studies have also shown that the association between BMI and tumors is dependent on age and sex with the effect being more pronounced in premenopausal women compared to their post menopausal counterparts. Higher consumption of dietary fats also poses a risk towards the above. [6] Increased levels of cholesterol and triglycerides in the body have also been positively correlated with obesity and predisposition towards gall bladder tumorigenesis. [30] Obesity leads to an imbalance of sex hormone and their receptors which may also increase the risk of cancers. [31] General as well as abdominal obesity have been associated with cancers of the biliary tract especially gall bladders. These factors have also been observed to aid in the development of gall

bladder stones. [32] The Asian population has a general tendency to exhibit a higher proportion of body fat leading to an increased risk of biliary tract cancers. Earlier reports have documented that both overweight and obese individuals are at an increased risk for developing gall bladder tumors with the risk percentage being 14% and 56% respectively. [33] Grade I, grade II and grade III obesity are characterized by 53%, 86% and 131% increased risk of gall bladder cancer in contrast to people having normal body weight and BMI. High body weight, waist diameter, waist to hip ratio and hip diameter have all been proved to be contribute towards the above. An increase of waist and hip diameter by 5cm has been shown to increase the risk of the disease by approximately 18%. [34] Furthermore, this effect has been studied to be more pronounced in women compared to men. Obesity and altered BMI imbalances metabolic homeostasis and contributes to hyperglycemia, hyperinsulinemia, dyslipidemia, hormonal imbalances and insulin resistance; all of which have a significant role in development of tumors. Obesity also elevates and activated IGF-1 and pro-inflammatory pathways which further promote dysregulated cell growth, division and differentiation. [35] Additionally, obesity and elevated BMI also contributes to an increased predisposition to diabetes mellitus. However, this effect is more prominent in patients with an increased body fat compared to an increased in muscle mass. Earlier studies have observed that individuals possessing an increased body weight and an elevated blood glucose levels are at an elevated risk of developing obesity mediated cancer. [36] Moreover, obesity accompanied by insulin resistance changes the levels of adipokines culminating in increased levels of leptin dependent cancer. Signaling crosstalk between leptin, glucose, IGF-1 and insulin has also been reported. [37-38] Excess fat which is stored in adipose tissues behaves as a tumor microenvironment further

contributing to carcinogenesis. [39] Obesity also increases the incidence of other gall bladder diseases including cholesterol gallstones further raising the probability of development of tumors. Obesity has been related to cholesterol overproduction and secretion aiding in development of gall stones mediated cancer. [5] Improper diet and lifestyle patterns are the main culprits responsible for deposition of excess body fat. Diets high in fatty and energy dense ingredients including fried, processed food and sugar sweetened food have all been associated with an increased BMI mediated risk of carcinogenesis. [26] Regular consumption of foods having greater than 225kcal/100gm have significantly been related to obesity. A positive energy balance has also been shown to elevate the availability of insulin like growth factor thereby aiding tumor development and progression. Moreover, controlling body weight and obesity has been reported to reduce the risk of several cancers. [40] Additionally, existing cancer therapy may also lead to a change in dietary and lifestyle preferences as well as requirements which may often be accompanied by weight gain if not monitored routinely. Therefore, excessive consumption of dietary sugars increase the possibility of obesity mediated insulin dependent gall bladder carcinoma.

#### **Sugar induces gallstones dependent gallbladder cancer**

Presence of gallstones is one of the important factors that predisposes towards gall bladder cancer. Patients with stones in the gall bladder are at four to seven times increased risk of developing cancer. Diagnoses of gall bladder stones followed by their removal are considered as effective strategies in prevention of the above. [5] The geographical variation of the disease can be attributed to the rates of development of gall stones in the respective areas. The staple diet followed in Northern India consisting of wheat and fats induces increased secretion of mucus which has been shown to be precipitated by gastric acids leading to release of cholecystokinin

thereby influencing gall bladder contraction and bile secretion. [14] Moreover, a family history of gall bladder disorders also increases the risk of an individual to cancer. Cholesterol gall stones generally occur due to over production of cholesterol accompanied by increased secretion of bile in the human body. These patients have an abnormal ratio of secondary to primary bile acids which help in formation of stones. [6] These are also elevated due to obesity, increased BMI and regular consumption of a caloric diet rich in sugar and fat. Moreover, consumption of sugar increases the risk of diabetes mellitus which is reported to elevate the risk to gall stones mediated cancer in the gall bladder. [39] Studies have shown that intake of a diet high in GI and GL increases the chances of development of gall stones. [41] Alterations in genes regulating bile synthesis and cholesterol metabolism including MDR3 and CYP7A1 have been implicated in the development of gall bladder disease which further predisposes to tumors under prolonged conditions. [42] Lower concentrations of High Density Lipoprotein and increased levels of plasma triglycerides lead to the formation of gallstones. A sugar rich diet elevates the secretion of bile by modulating the metabolism of lipoproteins. Elevated consumption of sweetened food increases the synthesis of Very Low Density Lipoprotein and triglycerides and

reduces HDL. Furthermore, carbohydrates also induce insulin response thereby again potentiating the risk of gall bladder carcinogenesis. Patients diagnosed with gall bladder stones have generally been found to possess increased levels of insulin. Hyperinsulinemia has indeed been correlated with the incidences of gallstones even in individuals with normal glucose levels. [43] Moreover, diet having increased levels of high GI and GL components have been shown to induce insulin resistance, hyperglycemia, glucose intolerance and type 2 diabetes mellitus mediated risk of gall stone disease dependent gall bladder cancer. Insulin has been observed to stimulate cholesterol biosynthesis thereby aiding in formation of gall stones. Also, patients having gall bladder stones usually possess an abnormal body weight helping in occurrence of the hyperinsulinemic response. Gall stone disease has also been correlated with metabolic disorders including heart diseases, obesity and cancer. [44] Additionally, gall stones trigger inflammatory pathways hence further accelerating tumor pathways. Therefore excess consumption of sweetened food further increases the possibility of gall bladder cancer via development of gall stones in addition to its direct role in obesity and insulin dependent carcinogenesis.

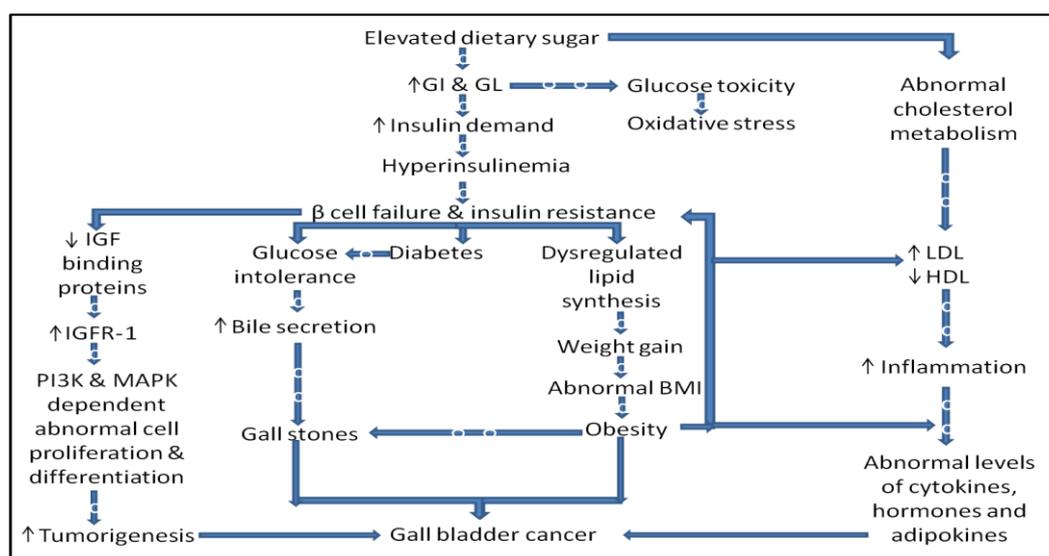


Figure 1: Sugar induces gall bladder cancer

Several studies have found hyperglycemia to increase the risk of tumors irrespective of other factors. Moreover, the relation of deregulated glucose homeostasis with incidences of non-Hodgkin's lymphoma, multiple myeloma, thyroid and bladder cancer is also well established. [45] The negative impact of glucose becomes apparent only when the concentration is above 6.1mmol/l. [46] General observation that diabetic patients are predisposed to several types of cancers may be due to the development of glucose intolerance and insulin resistance which may accelerate tumorigenesis in these patients. Sugar rich diet increases GI and GL dependent hyperinsulinemia and  $\beta$  cell failure which further predisposes towards the above. The improperly functioning pancreatic cells heightens the incidences of metabolic disorders including diabetes which induces increased bile secretion thereby aiding in development of gall bladder stones dependent tumorigenesis. Dysfunctional  $\beta$  cell also deregulates lipid synthesis promoting abnormal weight gain and increased BMI dependent gall bladder cancer. Furthermore, insulin resistance increases the probability of IGF-1 dependent activation of carcinogenic pathways leading to formation of gall bladder tumors. Additionally, increased consumption of dietary sugars promotes glucose toxicity and elevates the chances of increased LDL and inflammation dependent release of cytokines, adipokines and hormones, further contributing towards gall bladder carcinogenesis. Therefore regular consumption of a high sugar diet elevates the possibility of gall bladder tumors not only via insulin dependent pathways but also by increasing the chances of abnormal BMI and obesity mediated tumorigenesis. Moreover, increased sugar intake also predisposes towards formation of gall stones, a known contributor of gall bladder cancer (Figure 1).

## CONCLUSION

Diet has often been associated with the development and treatment of various diseases. The biochemical and functional components of a balanced diet has long been documented to play an important role in physiological well being of individuals. Sugar and artificially sweetened beverages have previously been associated with cancers of the colon, endometrium, breast, stomach and pancreas. Excessive consumption of sugar is responsible for several adverse health consequences. The present study describes the involvement of sugar in gall bladder cancer. Increased consumption of sugar enriched commodities raises the chances of insulin moderated cancer of the gall bladder. Elevated glucose is also linked to an increased predisposition towards higher BMI and obesity; both of which are also contributing factors towards gall bladder cancer. Additionally, diabetes is also a risk factor of development of gall bladder stones, thereby again facilitating the development of gall bladder cancers. Glucose itself is a tumor promoting factor due to its increased utilization by cancer cells for energy generation. The above factors along with the growth potentiating effects of insulin and insulin like growth factors may all together contribute to the advancement and severity of gall bladder tumorigenesis. Therefore limited consumption of sugar based food and regular consumption of a balanced diet may help in preventing the development of several chronic diseases especially gall bladder tumors.

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