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REFLECTION OF GLYCATED HAEMOGLOBIN (HbA1c) ON GLYCEMIC INDEX (GI) DURING DIABETES

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ABSTRACT

Glycosylated or Glycated hemoglobin (HbA1c): Hemoglobin to which glucose is bound. Glycosylated hemoglobin is tested to monitor the long-term control of diabetes mellitus. The level of glycosylated hemoglobin is increased in the red blood cells of persons with poorly controlled diabetes mellitus. Since the glucose stays attached to hemoglobin for the life of the red blood cell (normally about 120 days), the level of glycosylated hemoglobin reflects the average blood glucose level over the past 3 months. The normal level for glycosylated hemoglobin is less than 7%. Diabetics rarely achieve such levels, but tight control aims to come close to it. Levels above 9% show poor control, and levels above 12% show very poor control. It is commonly recommended that glycosylated hemoglobin be measured every 3 to 6 months in diabetes. The Diabetes Control and Complications Trial (DCCT) showed that diabetics who keep their glycosylated hemoglobin levels close to 7% have a much better chance of delaying or preventing diabetes complications that affect the eyes, kidneys, and nerves than people with levels 8% or higher. A change in treatment is almost always needed if the level is over 8%. Lowering the level of glycosylated hemoglobin by any amount improves a person's chances of staying healthy. Glycosylated hemoglobin is also known as glycohemoglobin or as hemoglobin A1C (the main fraction of glycosylated hemoglobin). The Glycemic Index (GI) is a value assigned to foods based on how slowly or how quickly those foods cause increases in blood glucose levels. Also known as "blood sugar," blood glucose levels above normal are toxic and can cause blindness, kidney failure, or increase cardiovascular risk. Foods low on the glycemic index (GI) scale tends to release glucose slowly and steadily. Foods high on the glycemic index release glucose rapidly. Low GI foods tend to foster weight loss, while foods high on the GI scale help with energy recovery after exercise, or to offset hypo- (or insufficient) glycemia. Long-distance runners would tend to favor foods high on the glycemic index, while people with pre- or full-blown diabetes would need to concentrate on low GI foods. Why? People with type 1 diabetes and even some with type 2 can't produce sufficient quantities of insulin—which helps process blood sugar—which means they are likely to have an excess of blood glucose. The slow and steady release of glucose in low-glycemic foods is helpful in keeping blood glucose under control.

KEYWORDS: Glycated hemoglobin, Glycemic Index, Fasting Blood Sugar, Postprandial Blood Sugar.

INTRODUCTION

The majority of healthy individuals, normal blood sugar levels are as follows: Between 4.0 to 5.4 mmol/L (72 to 99 mg/dL) when fasting. Up to 7.8 mmol/L (140 mg/dL) 2 hours after eating. For someone without diabetes, a fasting blood sugar on awakening should be under 100 mg/dl. Before-meal normal sugars are 70–99 mg/dl. “Postprandial” sugars taken two hours after meals should be less than 140 mg/dl. Those are the normal numbers for someone without diabetes.[1,2]

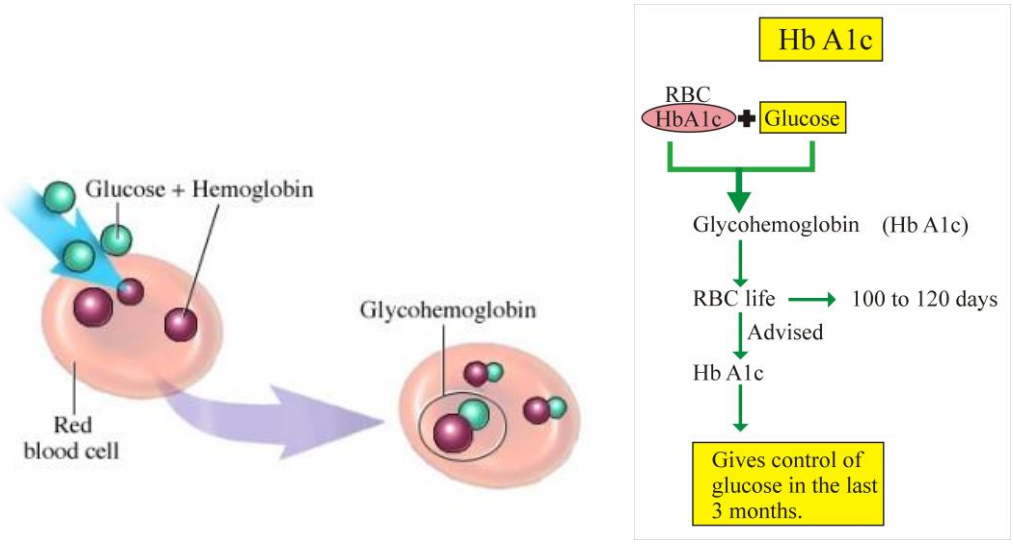

Figure-1: Glycosylated hemoglobin.

Glycated hemoglobin (hemoglobin A1c, HbA1c, A1C, or Hb1c; sometimes also referred to as being Hb1c or HGBA1C) is a form of hemoglobin that is measured primarily to identify the three-month average plasma glucose concentration. The test is limited to a three-month average because the lifespan of a red blood cell is four months (120 days). However, since red blood cells do not all undergo lysis at the same time, HbA1C is taken as a limited measure of three months. It is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. HbA1c is a measure of the beta-N-1-deoxy fructosyl component of hemoglobin. The origin of the naming derives from Hemoglobin type A being separated on cation exchange chromatography. The first fraction to separate, probably considered to be pure Hemoglobin A, was designated HbA0, the following fractions were designated HbA1a, HbA1b and HbA1c, respective of their order of elution. There have subsequently been many more sub fractions as separation techniques have improved. Normal levels of glucose produce a normal amount of glycated hemoglobin. As the average amount of plasma glucose increases, the fraction of glycated hemoglobin increases in a predictable way. This serves as an indicator that blood sugar is increasing and that action should be taken. In diabetes mellitus, higher amounts of glycated hemoglobin, indicating poorer control of blood glucose levels, have been associated with cardiovascular disease, nephropathy, neuropathy, and retinopathy. A trial on a group of patients with Type 1 diabetes found that monitoring by caregivers of HbA1c led to changes in diabetes treatment and improvement of metabolic control compared to monitoring only of blood or urine glucose. However, a trial designed specifically to determine whether reducing HbA1c below the normal 6%, using primarily insulin and sulfonylureas (both known to easily drive blood sugar too low), would reduce the rate of cardiovascular events in type 2 diabetes found higher mortality—the trial was terminated early. The negative outcomes may well have been a result of the treatment approach, primarily insulin and sulfonylureas, utilized in the "intensive" treatment group instead of LCHF, GlP-1 analogues & SGLT-2 inhibitors, none of which have these problems & lower cardiovascular mortality.[3,4]

Hemoglobin A1c was first separated from other forms of hemoglobin by Huisman and Meyering in 1958 using a chromatographic column. It was first characterized as a glycoprotein by Bookchin and Gallop in 1968. Its increase in diabetes was first described in 1969 by Samuel Rahbar. The reactions leading to its formation were characterized by Bunn and his coworkers in 1975. Glycated hemoglobin causes an increase of highly reactive free radicals inside blood cells. Radicals alter blood cell membrane properties. This leads to blood cell aggregation and increased blood viscosity which results in impaired blood flow.

Another way glycated Hb causes damage is via inflammation which results in atherosclerotic plaque (atheroma) formation. Free radical build-up promotes the excitation of Fe^{2+}-Hb through Fe^{3+}-Hb into abnormal ferryl Hb (Fe^{4+}-Hb). Fe^{4+} is unstable and reacts with specific amino acids in Hb to regain its Fe^{3+} oxidation state. Hb molecules clump together via cross-linking reactions and these Hb clumps (multimers) promote cell damage and the release of Fe^{4+}-Hb into the matrix of innermost layers (subendothelium) of arteries and veins. This results in increased permeability of interior surface (endothelium) of blood vessels and production of pro-inflammatory monocyte adhesion proteins, which promote macrophage accumulation in blood vessel surfaces ultimately leading to harmful plaques in these vessels. Highly glycated Hb-AGEs go through vascular smooth muscle layer and inactivate acetylcholine induced endothelium-dependent relaxation possibly through binding to nitric oxide (NO) preventing its normal function. NO is a potent vasodilator and also inhibits formation of plaque promoting LDLs (i.e. “bad cholesterol”) oxidized form. This overall degradation of blood cells also releases heme from them. Loose heme can cause oxidation of endothelial and LDL proteins

which results in plaques. A number of techniques are used to measure hemoglobin A1c.

Laboratories use: (1) High-performance liquid chromatography (HPLC): The HbA1c result is calculated as a ratio to total hemoglobin by using a chromatogram. (2) Immunoassay (3) Enzymatic (4) Capillary electrophoresis (5) Boronate affinity chromatography.

The use of hemoglobin A1c for monitoring the degree of control of glucose metabolism in diabetic patients was proposed in 1976 by Anthony Cerami, Ronald Koenig and coworkers. HbA1c is a term commonly used in relation to diabetes. This guide explains what HbA1c is, how it differs from blood glucose levels and how it's used for diagnosing diabetes. The term HbA1c refers to glycated haemoglobin. It develops when haemoglobin, a protein within red blood cells that carries oxygen throughout your body, joins with glucose in the blood, becoming 'glycated'. By measuring glycated haemoglobin (HbA1c), clinicians are able to get an overall picture of what our average blood sugar levels have been over a period of weeks/months. For people with diabetes this is important as the higher the HbA1c, the greater the risk of developing diabetes-related complications. HbA1c is also referred to as haemoglobin A1c or simply A1c. HbA1c refers to glycated haemoglobin (A1c), which identifies average plasma glucose concentration.[5,6]

When the body processes sugar, glucose in the bloodstream naturally attaches to haemoglobin. The amount of glucose that combines with this protein is directly proportional to the total amount of sugar that is in your system at that time. Because red blood cells in the human body survive for 8-12 weeks before renewal, measuring glycated haemoglobin (or HbA1c) can be used to reflect average blood glucose levels over that duration, providing a useful longer-term gauge of blood glucose control. If your blood sugar levels have been high in recent weeks, your HbA1c will also be greater.

HbA1c targets.
The HbA1c target for people with diabetes to aim for is: 48 mmol/mol (6.5%). Note that this is a general target and people with diabetes should be given an individual target to aim towards by their health team. An individual HbA1c should take into account your ability to achieve the target based on your day to day life and whether you are at risk of having regular or severe hypos.

HbA1c in diagnosis: HbA1c can indicate people with prediabetes or diabetes as follows:
Table-1: HbA1c range.

HbA1c	mmol/mol	%
Normal	Below 42 mmol/mol	Below 6.0%
Prediabetes	42 to 47 mmol/mol	6.0% to 6.4%
Diabetes	48 mmol/mol or over	6.5% or over

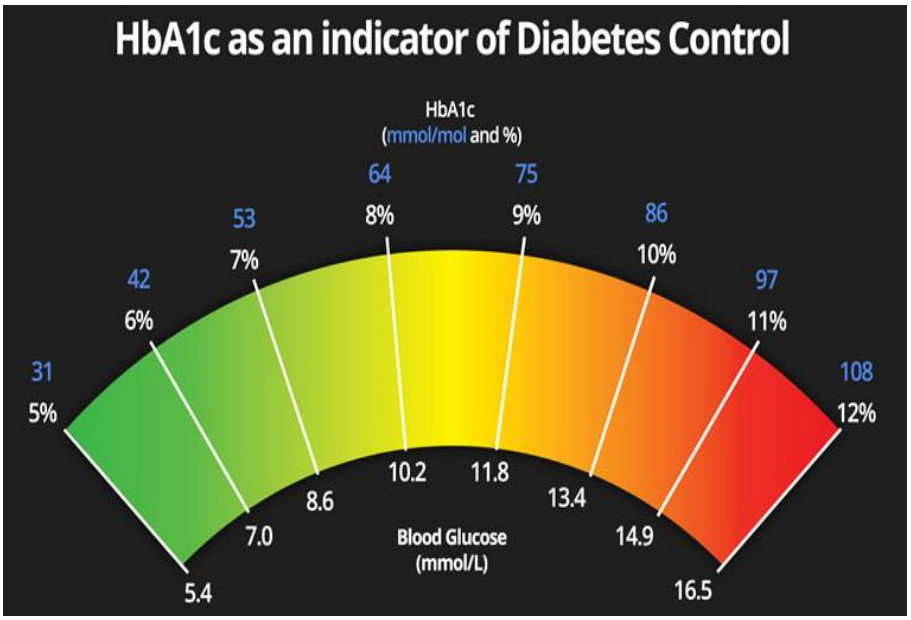

Figure-1: HbA1c percentage.

Two large-scale studies - the UK Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) - demonstrated that improving HbA1c by 1% (or 11 mmol/mol) for people with type 1 diabetes or type 2 diabetes cuts the risk of microvascular complications by 25%.[7,8]

Microvascular complications include: 1. Retinopathy 2. Neuropathy 3. Diabetic nephropathy (kidney disease)

Table-2: HbA1c & Glucose Blood Levels.

HbA1c (%)	HbA1c (mmol/mol)	Average Blood Glucose (mmol/L)
13	119	18 mmol/L
12	108	17 mmol/L
11	97	15 mmol/L
10	86	13 mmol/L
9	75	12 mmol/L
8	64	10 mmol/L
7	53	8 mmol/L
6	42	7 mmol/L
5	31	5 mmol/L

Research has also shown that people with type 2 diabetes who reduce their HbA1c level by 1% are: 19% less likely to suffer cataracts, 16% less likely to suffer heart failure, 43% less likely to suffer amputation or death due to peripheral vascular disease

How does HbA1c differ from a blood glucose level?: HbA1c provides a longer-term trend, similar to an average, of how high your blood sugar levels have been over a period of time. An HbA1c reading can be taken from blood from a finger but is often taken from a blood sample that is taken from your arm. Blood glucose level is the concentration of glucose in your blood at a single point in time, i.e. the very moment of the test. This is measured using a fasting plasma glucose test, which can be carried out using blood taken from a finger or can be taken from a blood sample from the arm. However, fasting glucose tests provide an indication of your current glucose levels only, whereas the HbA1c test serves as an overall marker of what your average levels are over a period of 2-3 months. HbA1c can be expressed as a percentage (DCCT unit) or as a value in mmol/mol (IFCC unit). Since 2009, mmol/mol has been the default unit to use in the UK. Note that the HbA1c value, which is measured in mmol/mol, should not be confused with a blood glucose level which is measured in mmol/l. Use our HbA1c conversion tool to help with switching between the two measurement units.[9,10]

When should HbA1c levels be tested?: Everyone with diabetes mellitus should be offered an HbA1c test at least once a year. Some people may have an HbA1c test more often. This may be more likely if you have recently had your medication changed or your health team are otherwise wishing to monitor your diabetes control more than once a year. Although HbA1c level alone does not predict diabetes complications, good control is known to lower the risk of complications.

How do blood glucose levels compare with HbA1c readings?: Table-2 shows how average blood sugar levels in mmol/L would be translated into HbA1c readings, and vice versa. It is important to note that because blood glucose levels fluctuate constantly, literally on a minute by minute basis, regular blood glucose testing is required to understand how your levels are changing through the day and learning how different meals affect your glucose levels. For people without diabetes, the normal range for the hemoglobin A1c level is between 4% and 5.6%. Hemoglobin A1c levels between 5.7% and 6.4% mean you have a higher chance of getting diabetes. Levels of 6.5% or higher mean you have diabetes.

The blood test for HbA1c level is routinely performed in people with type 1 and type 2 diabetes mellitus. Blood HbA1c levels are reflective of how well diabetes is controlled. The normal range for level for hemoglobin A1c is less than 6%. HbA1c also is known as glycosylated, or glycated hemoglobin.[11,12]

Table-3: HbA1c and glycated haemoglobin ranges

HbA_{1c}	eAG	HbA_{1c}	eAG
%	mmol/mol	mmol/L	mg/dL
5	31	13	119
6	42	14	130
7	53	15	140
8	64	16	151
9	75	17	162
10	86	18	173
11	97	19	184
12	108		

HbA1c: glycated haemoglobin. eAG: estimated average glucose

Carbohydrate is an essential part of our diets, but not all carbohydrate foods are equal. The Glycemic Index (GI) is a relative ranking of carbohydrate in foods according to how they affect blood glucose levels. Carbohydrates with a low GI value (55 or less) are more slowly digested, absorbed and metabolized and cause a lower and slower rise in blood glucose and therefore usually, insulin levels.

There are three classifications for GI: (1) Individual food portion [Low: 55 or less], Moderate: [56 – 69], High: [70+]

There is a real need to define the difference between a low GI diet and/or meal and a low GI food. Because a low GI food is defined as 55 or less, everyone has made

the reasonable assumption that a whole diet that averages 55 or less is a low GI diet. In fact the average Australian and American diets already have a GI of around 55–60 because we eat fruits and dairy foods which are naturally low GI. So, to reduce the risk of chronic disease, we believe we need to aim lower and suggest that 45 is a better cut-off point for a low GI diet.[13,14]

Thus for the whole day the classifications are: Low: 45 or less, Moderate: 46-59, High: 70+

Why 45?: We know from numerous observational cohort studies around the world that the daily average GI of the diet of people in the lowest quintile (20% of the population) is about 40–50. Similarly, in a meta-analysis in Diabetes Care of 15 experimental studies investigating the role of low GI diets in managing diabetes, the daily average GI was 45. Since this average GI has been proven to have significant health benefits in people with existing diabetes and in reducing the risk of chronic diseases like heart disease and diabetes, and importantly, people can and do achieve it in real life, we believe a GI of 45 or less is what we all need to be aiming for.

Glycemic Index (GI) is a scale, which helps in ranking the carbohydrate rich foods, depending on how they affect blood glucose levels in a span of 2 - 3 hours after having food. The food having a higher GI breaks down quickly and shoots up your blood sugar levels rapidly. While the food having a lower GI takes a longer time to get digested and absorbed, resulting in slower and gradual changes in blood sugar levels. The glycemic index or glycaemic index (GI) is a number associated with the carbohydrates in a particular type of food that indicates the effect of these carbohydrates on a person's blood glucose (also called blood sugar) level. A value of 100 represents the standard, an equivalent amount of pure glucose. The GI represents the rise in a person's blood sugar level two hours after consumption of the food. The glycemic effects of foods depends on a number of factors, such as the type of carbohydrate, physical entrapment of the carbohydrate molecules within the food, fat and protein content of the food and organic acids or their salts in the meal. The GI is useful for understanding how the body breaks down carbohydrates and takes into account only the available carbohydrate (total carbohydrate minus fiber) in a food. Glycemic index does not predict an individual's glycemic response to a food, but can be used as a tool to assess the insulin response burden of a food, averaged across a studied population. Individual responses vary greatly. The glycemic index is usually applied in the context of the quantity of the food and the amount of carbohydrate in the food that is actually consumed. A related measure, the glycemic load (GL), factors this in by multiplying the glycemic index of the food in question by the carbohydrate content of the actual serving. Watermelon has a high glycemic index, but a low glycemic load for the quantity typically consumed. Fructose, by contrast, has a low glycemic index, but can have a high glycemic load if a large quantity is consumed. GI tables are available that list many types of foods and their GIs. Some tables also include the serving size and the glycemic load of the food per serving.[15,16]

A practical limitation of the glycemic index is that it does not measure insulin production due to rises in blood sugar. As a result, two foods could have the same glycemic index, but produce different amounts of insulin. Likewise, two foods could have the same glycemic load, but cause different insulin responses. Furthermore, both the glycemic index and glycemic load measurements are defined by the carbohydrate content of food. For example, when eating steak, which has no carbohydrate content but provides a high protein intake, up to 50% of that protein can be converted to glucose when there is little to no carbohydrate consumed with it. But because it contains no carbohydrate itself, steak cannot have a glycemic index. For some food comparisons, the "insulin index" may be more useful.

A1C Chart based on ADAG formula

A1C-Derived Average Glucose (ADAG) Study;
eAG in mg/dl = (28.7* hba1c)-46.7 or
eAG in mmol/l = (1.59 x HbA1c)-2.59

A1C	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1
mg/dl	68	71	74	77	80	82	85	88	91	94	97	100
mmol/l	3.8	3.9	4.1	4.3	4.4	4.6	4.7	4.9	5.1	5.2	5.4	5.6
A1C	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0	6.1	6.2	6.3
mg/dl	103	105	108	111	114	117	120	123	125	128	131	134
mmol/l	5.7	5.8	6.0	6.2	6.3	6.5	6.7	6.8	6.9	7.1	7.3	7.4
A1C	6.4	6.5	6.6	6.7	6.8	6.9	7.0	7.1	7.2	7.3	7.4	7.5
mg/dl	137	140	143	146	148	151	154	157	160	163	166	169
mmol/l	7.6	7.8	7.9	8.1	8.2	8.4	8.5	8.7	8.9	9.0	9.2	9.4
A1C	7.6	7.7	7.8	7.9	8.0	8.5	9.0	9.5	10.0	11.0	12.0	13.0
mg/dl	171	174	177	180	183	197	212	226	240	269	298	326
mmol/l	9.5	9.7	9.8	10.0	10.2	10.9	11.8	12.5	13.3	14.9	16.5	18.1
Super Optimal		Optimal		Normal		Pre Diabetes		Diabetes		Dangerous		

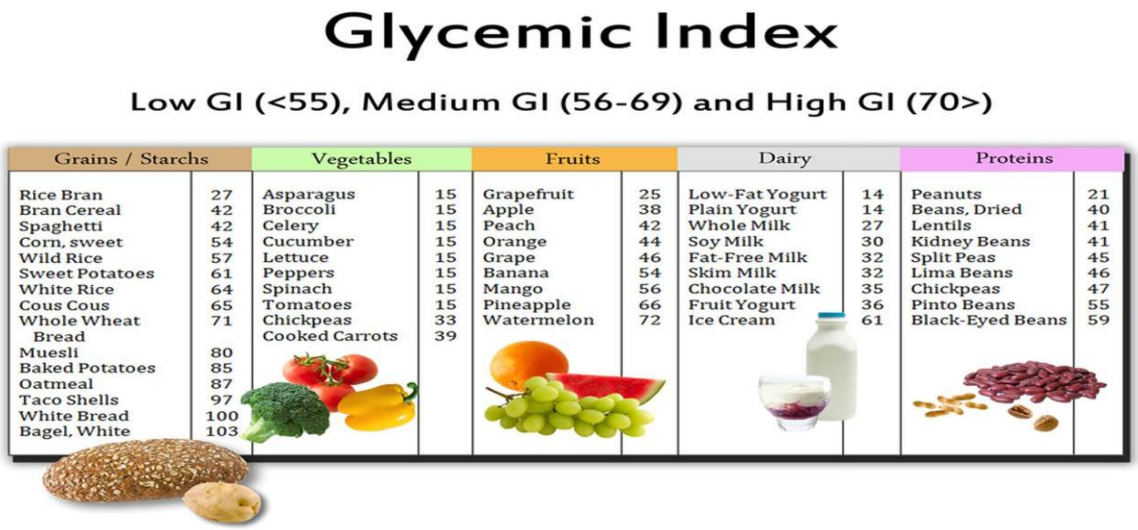

Figure-2: Chart of Glycated hemoglobin and Glycemic Index.

Glycemic index charts often give only one value per food, but variations are possible due to: 1. ripeness (riper fruits contain more sugars increasing GI) 2. cooking methods (the more cooked, or over cooked, a food, the more its cellular structure is broken, with a tendency for it to digest quickly and raise GI more) 3. processing (e.g., flour has a higher GI than the whole grain from which it is ground as grinding breaks the grain's protective layers) and the length of storage. Potatoes are a notable example, ranging from moderate to very high GI even within the same variety. More importantly, the glycemic response is different from one person to another, and also in the same person from day to day, depending on blood glucose levels, insulin resistance, and other factors. The glycemic index only indicates the impact on glucose level two hours after eating the food. People with diabetes have elevated levels for four hours or longer after eating certain foods.

High-glycemic foods cause a spike in blood sugar and increase the amount of insulin in your body. A recent study found that high-glycemic foods may be a major risk factor for developing lung cancer — and a whole subset of cancers, including breast, prostrate, and colon, which are highly responsive to insulin. See below for a list of high- and low-glycemic foods, so you can know which foods to avoid, and which to favor.[17,18]

High-Glycemic Foods (70 and above): Sugar, Flour, Rice, White potatoes, Some fruits: bananas, grapes, cherries, watermelon, Raisins, Many breakfast cereals, including puffed rice and corn flakes, Bread, Soda, Cookies and crackers glucose (dextrose, grape sugar), high fructose corn syrup, white bread (only wheat endosperm), most white rice (only rice endosperm), corn flakes, extruded breakfast cereals, maltose, maltodextrins, white potato.

Medium Glycemic Foods (56–69): white sugar or sucrose, not intact whole wheat or enriched wheat, pita bread, basmati rice, unpeeled boiled potato, grape juice, raisins, prunes, pumpernickel bread, cranberry juice, regular ice cream, banana, sweet potato.

Low-Glycemic Foods (55 or less): Sweet potatoes, Many vegetables, including leafy greens, asparagus, cauliflower, Steel-cut oatmeal, Farrow, Quinoa, Legumes, including lentils, chickpeas, Ezekiel bread, Skim milk, Reduced-fat yogurt, Sesame seeds, peanuts, flax seeds, fructose; beans (black, pinto, kidney, lentil, peanut, chickpea); small seeds (sunflower, flax, pumpkin, poppy, sesame, hemp); walnuts, cashews, most whole intact grains (durum/spelt/kamut wheat, millet, oat, rye, rice, barley); most vegetables, most sweet fruits (peaches, strawberries, mangos); tagatose; mushrooms; chilis.[19,20]

CONCLUSION

Importance of Glycemic index: Our body has an obligatory requirement for glucose depending on metabolic demands of our body. It is usually around 200gms/day. Our brain completely depends on glucose and oxygen. Maintaining a constant blood glucose level is important for our health and well being. Both low and high levels can be dangerous, sometimes even fatal. If you are feeling lethargic and hungry during the day after hard work, it is most likely due to low blood glucose level. Blood sugar level below 40mg/dl (known as 'Hypoglycemia' in medical terms) causes coma, stupor and even death. Blood sugar level more than 180mg/dl (known as 'Hyperglycemia' in medical terms) causes long-term complication of diabetes mellitus. Levels above 300 to 500 mgs/dl can cause acidosis and also lead to a state of coma Excess glucose that is stored is most often converted to fat. Food with high GI makes you initially feel very energetic but as the fat increases, with time, it makes you lethargic. Research has shown that maintaining blood sugar levels, from a state where the blood sugar levels were fluctuating, does pay-off in the long run. The following are the benefits.

Lowers risk of heart disease, Prevents Type 2 diabetes (Genetically determined diabetes where the individual body is resistant to insulin actions), Help to evade serious side effects, if you have diabetes, Curbs appetite, so you lose weight, Helps to feel more energetic and this is important for a person's well being.

Glycemic Load (GL) of Food – While GI indicates the amount of glucose and the quality of food, GL indicates the quantity of food and it is calculated as: GL = GI × Amount of Carbohydrates in gms/100.

GL of 10 or below are considered low whereas 20 or above are considered high. So if you love to eat food with High GI then try and consume very little for the purpose of your satiety, so that GL is kept less than 10.

Glycemic Index and Weight Loss: Glycemic Index diet programs are highly successful for weight loss and all diet plans for this are based on GI. For sustaining weight loss the person should have some knowledge about the foods that have high GI and avoid them. The common food includes refined carbohydrates (white bread), sweets, puddings, desserts, cakes, potato and rice to name a few.

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