# Section 5

**Metabolism, Lipids, and Obesity**

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>78.</td>
<td><strong>Current Concepts in Etiopathogenesis of Obesity</strong></td>
<td>CL Nawal, Abhishek Yadav</td>
</tr>
<tr>
<td>79.</td>
<td><strong>Dilemma in the Management of Hyperuricemia</strong></td>
<td>Brijesh Kumar, Mohammad Aqique</td>
</tr>
<tr>
<td>80.</td>
<td><strong>Risk Factors for Gout Flare</strong></td>
<td>Udas Chandra Ghosh, Asish Mondal</td>
</tr>
<tr>
<td>81.</td>
<td><strong>Vitamin D—A Hope or Hype?</strong></td>
<td>Sanjay Dash</td>
</tr>
<tr>
<td>82.</td>
<td><strong>Hyponatremia—An Update on Diagnosis and Treatment</strong></td>
<td>Samir Sahu</td>
</tr>
<tr>
<td>83.</td>
<td><strong>Osteoporosis “The Battle Still to Overcome”</strong></td>
<td>Niraj Lodha, Divyansh Mathur, Naman Lodha</td>
</tr>
<tr>
<td>84.</td>
<td><strong>Intermittent Fasting in Obesity—Hope or Hype?</strong></td>
<td>Soumitra Ghosh</td>
</tr>
</tbody>
</table>
Abstract

Obesity is one of the most common chronic communicable diseases in the world. It is not only accumulation of adipose tissue in the body, but also a defect in homeostasis of our energy. Many factors contribute to etiology of obesity, but a complex interface between hormones, environment, and genetics play a major role. For a better understanding of pathogenesis of obesity, it can be grouped into energy consumption, energy utilization, and role of genetics. Serotonin, Dopamine, and some gut hormones influence homeostatic and hedonic pathways that control intake of energy. Reduction in resting energy expenditure, activity energy expenditure, and diet induced thermogenesis contribute to obesity via low energy utilization. Leptin gene discovery was a big breakthrough in molecular genetics research on obesity. Obesity can be a result of polygenic factors, or single gene disorders apart from various syndromes which have obesity as their predominant manifestation. Being a modern epidemic, obesity incurs significant cost to world economy and targeted therapies as per genetic profiling of individuals are the need of future.

Introduction

Obesity is a pandemic of the 20th century. It is among the one of the most common chronic non-communicable diseases throughout the world. Obesity is not only the accumulation of adipose tissue leading to weight gain; it is rather a defect in our energy homeostasis. Obesity is increasing at an alarming rate both in developed and developing countries. The etiology of obesity is multifactorial, which involves a composite interface among hormones, the environment, and genetics. The aim of this article is to review the etiopathogenesis and the role of genetics in obesity.

Etiology and Pathogenesis of Obesity

Human beings consume food as energy, which is stored as well as utilized in maintaining the basal metabolism of the body. Reduction in physical activities due to sedentary lifestyles leads to excessive storage of energy of which 60–80% is as fat or adipose tissue. It leads to obesity, the fifth most common cause of non-communicable disease. In the pathogenesis of obesity, multiple factors play a role, which include lifestyle affecting reduced energy expenditure, hormones affecting energy intake and the part of genetics. Gastrointestinal hormones, adipokines, and various genes including beta-3-adrenergic receptor gene peroxisome-proliferator-activated receptor gamma 2 (PPAR-γ) gene and other genetic polymorphism majorly regulates the pathophysiology of obesity.

Pathogenesis of obesity can be divided into three ways:

- Energy consumption
- Energy utilization
- Role of genetics

Energy Consumption

Homeostatic and hedonic are the two pathways that control intake of energy. When the body is deficient in
energy, the homeostatic mechanisms stimulate the appetite, the hypothalamus as well as brainstem acts as central regulators and senses the signals including leptin, insulin, hormones, and vagal afferents. Hedonic pathway is a mediator of rewarding aspects for food intake. When both pathways and systems are uncontrolled, it leads to obesity. Two neurotransmitters serotonin and dopamine play a vital role in the energy intake.6

**Serotonin and dopamine:** Serotonin is a neurotransmitter of homeostatic pathways. Reduction in signaling by serotonin in the hypothalamus contributes to the origin of obesity as it affects the negative feedback from the food intake, which leads to over consumption. Various studies explain a strong link between hypo-serotonin environment and development of obesity.7,8 As far as dopamine is concerned, decrease in the dopaminergic signaling also promotes overconsumption. As dopamine is a reward hormone, thus lower reward sensations lead to its effects.9

**Gastrointestinal hormones:** Gut-brain axis or feedback system plays an important role to maintain hunger and satiety. Several gut hormones: ghrelin, cholecystokinin, peptide YY, glucagon like peptide-1, oxyntomodulin are involved as messengers in this axis. Along with the function related to food digestion, these hormones equally affect specific brain areas modulating food or energy intake.

Ghrelin, the only hormone that stimulates hunger is produced by the endocrine cells of gastric fundus.10 Ghrelin binds to the growth hormone receptor which is highly expressed in the hypothalamus. In obese subjects, the fasting levels of ghrelin are low as compared to normal weight controls. Diet induced obesity mainly occurs due to ghrelin resistance, which arises as there is reduction in the NPY/AgRP responsiveness to plasma ghrelin leading to suppression of neuroendocrine ghrelin axis.11 Other intestinal hormones are anorexigenic which includes glucagon-like peptide 1 (GLP1), peptide YY (PYY), and cholecystokinin (CCK).12 The over consumption of meals in obese humans is strongly associated with the reduction of activity of these anorexigenic hormones.13

**Leptin:** The revolutionary discovery of leptin occurred in 1994. It is synthesized in white adipose tissues. The level of leptin in the body correlates with the fat mass. The leptin levels in plasma and CSF will be higher in a person with excess body fat.14 Leptin acts as an informant to the brain about the reserved adipose energy. It crosses the blood brain barrier and inhibits orexigenic NPY/AgRP neurons and stimulates POMN-expressing anorexigenic neurons in the hypothalamus. Responsiveness to leptin decreases in obesity. Leptin resistance not only affects the energy consumption but also decreases insulin sensitivity and cognition. Leptin levels are higher in obese individual due to increased production by adipocytes to compensate the low responsiveness. Inability or defect in crossing the blood brain barrier is also associated with reduced feedback by leptin.15 Low levels of leptin or resistance of leptin impairs its ability to counterbalance the effect of ghrelin.16

**Insulin:** Sedentary lifestyle leads to increased risk of diabetes. It is associated with raised insulin levels due to insulin resistance. Hyperinsulinemia lead to weight gain and obesity because of a physiological property of insulin. Beside the effect of lifestyle factors, the pathway to obesity needs hyperinsulinemia as an important moderator in translating an unworthy lifestyle turning into gain of weight.17 The insulin resistance, which causes hyperinsulinemia and later obesity, occurs mainly due to defect in insulin signaling in adipocytes as well as downregulation of GLUT4.18

As a pleiotropic effect, raised insulin levels lead to more synthesis of adipocytes from preadipocytes. It also promotes lipogenesis by stimulating ADD-1/SREBP-1c which plays the role of regulating fatty acid synthesis and lipogenesis in hepatocytes and adipocytes.19 With the recognition of insulin resistance and hyperinsulinemia as the potential mechanism of obesity has come increases investigation and research aimed at elucidating potential insulin sensitizing agents. Thus, it’s established that insulin receptor function is vital for energy homeostasis.

**Circadian rhythms:** Nature is always dominant. Biological rhythms play an important role in virtually all aspects of life. These rhythms are controlled in large part by circadian clocks, a molecular mechanism which is intrinsically maintained to control these biological rhythms and adapt or condition the human beings to its changing environment. Two types of clocks exist, the central and the peripheral clock. Suprachiasmatic nucleus (SCN) of the brain possesses the central clock, which responds with light. Other than SCN (including those clocks found
in other cells of the central nervous system) all other cells possess peripheral clocks which work under the influence of neurohormonal changes.

Changing lifestyles, late night working shifts alters the functioning of these clocks leading to poor anticipation of diurnal variations in the environment of the body. It could be circulating levels of glucose, fatty acids, or hormones including insulin and triglycerides. Altered molecular mechanism in the adipocytes leads to accumulation of fat and finally obesity.20

**Gut bacteria:** Our gut consists of numerous bacteria. These play an important role in digestion of food. Recent research indicates that gut microbiota also plays a part in pathogenesis of obesity. Low fecal diversity markedly leads to overall adiposity and dyslipidemia along with low-grade inflammation.21 In obese individuals, *Firmicutes* strain of bacteria are increased and *Bacteroidetes* strain is markedly low in fecal samples, in comparison to lean individuals.22 It suggests, overweight/obesity are preceded by differences in the gut microbiota. Several other studies too found change in gut bacteria composition in obese individuals but high ratio of *Firmicutes:Bacteroidetes* in obese individuals with excess *Bacteroidetes* during weight loss is not consistent.23,24

**Energy Utilization**

Low energy expenditure (LEE) contributes to development of obesity is always suggested. Reduction in resting energy expenditure (REE), activity energy expenditure (AEE), and diet induced thermogenesis (DIT) all lead to storage of energy leading to weight gain and obesity.25 A review was done Carneiro et al. to see the comparison between energy expenditures measures and its components, namely REE, AEE, and diet-induced thermogenesis (DIT), playing role in obese and non-obese adults. Results clearly shown the obese individuals require higher absolute REE and total EE. Although no difference is seen when fat free mass and metabolically active components are involved. However, AEE and DIT can be low obese individuals, because of sedentary habits, poor physical activity, and high intake of fat.26 Reduction in exercise associated thermogenesis and non-exercise associated thermogenesis significantly contributes weight gain in obesity. Nowadays various phenotypes of obesity like sarcopenic obesity and normal weight obesity are associated with energy expenditure in comparison to lean and thin individuals.27

**Flowchart 1:** A schematic diagram showing integration of long-term and short-term regulatory signals influencing energy intake and expenditure

Weight gain is also associated with drugs as anti-psychotics, tricyclic antidepressants, lithium, steroids, antiepileptics and insulin. Smoking cessation, due to nicotine withdrawal also causes weight gain (Flowchart 1).

There is also a role of endocrine disruption chemicals (EDCs) in obesity as their exposure is associated with stimulation of adipogenesis and changes in insulin secretion, sensitivity, and metabolism of liver. EDCs like perfluorinated chemicals (PFCs) and bisphenol-A (BPA) are linked with accumulation and maintenance of excess body fat in many studies.

**Role of Genetics in Obesity**

For long it was proposed that obesity may also be caused due to innate biological mechanisms under influence of genetic factors. In 1977, Feinleib et al. established the fact through their study that familial aggregation for obesity results from genetic influence.28 Stunkard and colleagues performed two studies in 1986 and 1990 amongst twins offering compelling evidence that one’s weight could be determined by one’s parentage. The leptin gene discovery in 1994 was a big breakthrough in molecular genetics research on obesity. Twin study suggests that heritable factors are responsible for 40–85% variation in body fat. Risk of obesity in children is 2.5–4 times high in single parent obesity, whereas it was 10 times for both parents being obese.29,30
The influence of genetic variables can be significantly reduced by high level of physical activity and environmental modifications. Mutations in various other molecules responsible for energy balance via the hypothalamus/melanocortin pathway have been described, which contribute to obesity.32

**Polygenic obesity:** Genetic factors play a permissive role and interact with environmental factors to produce obesity. Genome wide association studies (GWAS) in European population focused on 70–80% common variations using single nucleotide polymorphism (SNP). Variation in intron-1 of Fat Mass and Obesity associated (FTO) gene has been identified as contributor to polygenic obesity. MC4R gene was associated with hyperphagia and early onset diabetes. SH2B1 (Src-Homology-2 [SH2] domain containing putative adaptor protein-1) is associated with increased serum leptin. Other genes, which are highly expressed in hypothalamus and associated with obesity are KCNT1 (potassium channel tetramerization domain-containing 1), GNPDA2 (glucosamine-6-phosphate deaminase-2), MTC2 (mitochondrial carrier homolog 2), SDC4AG8 (serologically defined colon cancer antigen 8), FAIM2 (Fas Apoptotic Inhibitory Molecule 2) and PRL (prolactin).34,35

One peripheral acting gene TFAP2B (transcription factor activating enhancer-binding protein 2β) is preferentially expressed in adipose tissue, which is involved in glucose transport, lipid accumulation, and adiponectin expression. New GWAS have started to appear in East Asian population promising discovery of further more loci related to genetic forms of obesity.

**Syndromic obesity:** A variety of syndromes with obesity as their primary manifestation have been identified. Some of the important ones with their main features have been described in Table 1.

**Monogenic obesity:** These are single gene disorders causing a highly penetrant form of disease. These genes affect the leptin/melanocortin pathway in central nervous system and have been described in Table 2.

Even after discovery of these numerous genetic factors, only a small fraction of obesity cases could be attributed to them. Variations in FTO and MC4R are two most important genes that are strongly linked to obesity, but still account for less than 2% of variance in adult BMI. It is assumed that there must be a missing link in the heritability of obesity, and more GWAS are underway to search for them. Discovery of these factors would open up new possibilities for novel drugs, diagnosis, treatment, and prevention of obesity.

### Table 1

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Obesity onset (type)</th>
<th>Clinical features</th>
</tr>
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<tbody>
<tr>
<td>Albright hereditary osteodystrophy (pseudohypoparathyroidism type 1a)</td>
<td>GNAS1</td>
<td>Early (generalized)</td>
<td>Short stature, round face, cognitive delay, skeletal abnormalities along with obesity</td>
</tr>
<tr>
<td>Alström</td>
<td>ALMS1</td>
<td>Age 2–5 years (central)</td>
<td>Obesity with acanthosis nigricans, normal cognition, blindness, deafness, chronic nephropathy, type 2 diabetes, and cirrhosis</td>
</tr>
<tr>
<td>Bardet-Biedl syndrome</td>
<td>BBS1, 2, 3...</td>
<td>Age 1–2 years (central)</td>
<td>Obesity with cognitive delay, polydactyly, retinitis pigmentosa, hypogonadism and renal dysfunction</td>
</tr>
<tr>
<td>Beckwith-Wiedemann</td>
<td>Multiple</td>
<td></td>
<td>Obesity with intolerance of fasting, hyperinsulinemic hypoglycemia</td>
</tr>
<tr>
<td>Carpenter</td>
<td>RAB23</td>
<td>(Central)</td>
<td>Short stature with obesity, brachycephaly, polydactyly, umbilical hernia, mental retardation high-arched palate, cryptorchidism, male hypogonadism</td>
</tr>
<tr>
<td>Cohen</td>
<td>COH1</td>
<td>Mild-childhood (central)</td>
<td>Hypotonia and failure to thrive in infancy, mental retardation, microcephaly, prominent central incisors; long, thin fingers, and toes</td>
</tr>
<tr>
<td>Prader-Willi</td>
<td>NDN, SNRPN</td>
<td>Age 1–3 years (generalized)</td>
<td>Hypotonia, upslanting eyes, cognitive delay and behavioral abnormalities along with obesity</td>
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</tbody>
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TABLE 2  Single gene disorders causing obesity

<table>
<thead>
<tr>
<th>Disorder (Gene)</th>
<th>Gene</th>
<th>Clinical feature</th>
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<tr>
<td>Leptin deficiency (various mutations interfering with synthesis or secretion of leptin)</td>
<td>LEP</td>
<td>Severe early-onset obesity, hypometabolic rate, hyperphagia, pubertal delay, impaired glucose tolerance, hypothalamic hypogonadism, frequent infections. Very low or undetectable leptin levels. Obesity and hyperphagia respond to replacement with exogenous recombinant leptin</td>
</tr>
<tr>
<td>Leptin receptor deficiency</td>
<td>LEPR</td>
<td>Severe early-onset obesity, hypometabolic rate, hyperphagia, pubertal delay, hypothalamic hypogonadism. Leptin levels are high but are proportional to the degree of obesity, so they are not a useful marker for this defect. No response to treatment with exogenous leptin</td>
</tr>
<tr>
<td>Leptin dysfunction (biologically inactive leptin)</td>
<td>LEP (LEP p.D100Y)</td>
<td>Severe early-onset obesity, hyperphagia. Leptin levels are elevated (consistent with degree of obesity) but biologically inactive. Obesity and hyperphagia respond to treatment with exogenous recombinant leptin</td>
</tr>
<tr>
<td>Pro-opiomelanocortin deficiency</td>
<td>POMC</td>
<td>Adrenal insufficiency (typically presenting in the neonatal period), severe early-onset obesity, hyperphagia, and red hair in Caucasians</td>
</tr>
<tr>
<td>Pro-protein convertase 1/3 deficiency</td>
<td>PCSK1, also known as prohormone convertase 1</td>
<td>Early-onset obesity, diarrhea, abnormal glucose homeostasis, hypogonadotropic hypogonadism, hypocortisolism, elevated plasma proinsulin and POMC</td>
</tr>
<tr>
<td>Melanocortin receptor 4 haploinsufficiency</td>
<td>MC4R</td>
<td>Early-onset moderate to severe obesity, early-onset hyperphagia, increased bone density, accelerated linear growth, severe hyperinsulinemia, mild central hypothyroidism</td>
</tr>
<tr>
<td>Melanocortin 2 receptor accessory protein 2</td>
<td>MRAP2</td>
<td>Severe nonsyndromic early-onset obesity (probably very rare)</td>
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Conclusion

A complex interaction between genetic factors, environmental factors, and human behavior influences pathogenesis of obesity. Obesity is a modern epidemic and incurs massive health-care cost to world economy. Even with all recent advances, less than 2% of interindividual variations in BMI can be attributed to discover established gene loci. Along with well-known principles of prevention and control of obesity, targeted therapies as per genetic profile of the individual are of the need in future.

References

CHAPTER 79

Dilemma in the Management of Hyperuricemia

Brijesh Kumar, Mohammad Aquiqe

Abstract

Introduction: Hyperuricemia is a condition which is due to excess accumulation of uric acid in the blood either due to overproduction or under excretion or both.

Clinical Manifestations: Four stages asymptomatic, acute gout, inter-critical, and advanced gout.

Management: Asymptomatic individual usually does not require treatment but symptomatic patient may require pharmacological and non-pharmacological treatment.

Conclusion: Symptomatic patient with or without complications may require treatment.

Introduction

Hyperuricemia is a disorder of purine metabolism in which last product of metabolism, that is, uric acid is increased either due to overproduction or under excretion or both of the process. Hyperuricemia is defined as serum urate concentration 405 μmol/L (6.8 mg/dL) [serum urate level of 7.0 mg/dL (415 μmol/L) and in men 5.7 mg/dL (340 μmol/L) for women].

Causes

- Urate under excretion Primary hyperuricemia— or idiopathic; Secondary hyperuricemia, due to— inhibition of urate secretion, abnormally decrease in renal function.
  Drugs which causing under excretion— ethumbutol salicylate and laed etc.
- Urate overproduction—
  - Primary hyperuricemia due to enzyme defect.
  - Secondary hyperuricemia due to
    - purine rich diet,
    - increase nucleotide turnover,
    - ATP degradation
      - Glucose-6-phosphatase deficiency,
      - Tissue hypoperfusion
      - Over alcohol intake.

Hyperuricemia is related with cardiovascular conditions, obesity, and metabolic syndrome etc.

Clinical Manifestation

Stage 1: Asymptomatic hyperuricemia: this condition is most common but does not constitute disease, if urate deposited then damage the organ directly but not found in all and evidence suggests that no need of treatment in this stage.

Stage 2: Acute gout—in this stage patient develop local deposition of urate particles and any minor trauma can produce release of urate crystals in joint space and condition of acute gout.

Stage 3: Intercritical period.

Stage 4: Advanced gout. Chronically deposition of urate crystals and patient develop stiff joint. This progression is variable from person to person.
Complications
Most common is gouty arthritis and other complications are nephrolithiasis, urate nephropathy, and uric acid nephropathy.10-12

Investigations
- Twenty-four hours uric acid excretion: Normal uric acid excretion is 600 mg/day in a purine-free diet individual if this value exceeds then it suggests that hyperuricemia is due to overproduction and if this value decreases then it means hyperuricemia is due to under excretion of uric acid, but if patient on regular diet then normal uric acid excretion value up to 800 mg/dL.
- Complete blood count (CBC), lipid profile, calcium, and phosphate levels. These laboratory studies assess for underlying disease leading to elevated uric acid.
- Joint radiographs for joint swelling or deformity etc.13
- Renal ultrasound is done for uric acid stones.
- Consider joint aspiration to evaluate for uric acid crystals, look for negatively birefringent less polarized microscopy.13

Treatment
Hyperuricemia does not constitute a disease condition. Treatment depends on cause and potential consequences and complications in every patient.18
- Asymptomatic hyperuricemia is mainly treated by non-pharmacological interventions like lifestyle modifications, purine free diet, weight reduction, decrease in the quantity of alcohol soft drink consumption.18 As mentioned earlier metabolic syndrome is a risk factor for hyperuricemia so treat the accompanying diabetes mellitus, hyperlipidemia, high blood pressure and morbid obesity.
  - Body Weight and Exercise: In a cross-section analysis it is found that with increase in body weight serum level of uric acid increases and also positive correlation with metabolic syndrome. So weight reduction done via dietary modification and exercise can decrease the serum uric acid level also reducing the risk of gout. Gradual decrease in body weight is more valuable than drastic reduction. Because abrupt fall in weight can lead to ketosis and in turn this will lead to increase absorption of uric acid and ultimately increase in level of uric acid in serum.14-17
  - Dehydration and Rehydration: Uric acid excretion is directly proportional to urine flow so one of the risk factor for gout is dehydration and thus gout patients are advised to take lots of fluid. If taking adequate amount of fluid 24 hours before gouty flare then there is definite decrease in gout attacks.16,19
  - Dietary Factors: An open labeled study suggest that there is some role of dietary factors in prevention of hyperuricemia and gout. But some also have ability to increase the level of uric acid. It is also found that those patient who are having hyperuricemia have a poor diet.20
  - Purine-Rich Foods: Those foods which are rich in purine, on ingestion can increase the serum uric acid level. But not all purine rich foods lead to increase serum uric acid level.
    Duration of food ingestion is also important. For example, if taking diet which is rich in purine for 7–10 days then only slight change level of serum uric acid and for some duration only, and also if we are taking diet which is low in purine content for 1–2 weeks then only 1–2 mg/dL decrease in serum uric acid. So this means strict restriction of purine derivative foods in diet has not much role in uric acid control.21
  - Fructose: Fructose is the only sugar in fruits, which can increase the level of serum uric acid. Thus, fructose consumption is one of the factors in recent, which increases the prevalence of gout nowadays.22
  - Dairy Products: Dairy product reduces the risk of development of gout because the can decrease the serum uric acid level, which is suggested by some studies also.23,24
  - Cherries: Cherry from many decades used as alternative therapy for gout. Gout ingestion lead to decrease pain of gout. First study done in 1950.25
  - Mediterranean Diet: This diet is very helpful in patients of diabetes and coronary disease etc. It contains legume, cherry, olive oil, moderate fish consumption, etc.26
  - Alcohol: Alcohol promotes hyperuricemia it increases urate level by increased production by
the accelerating the hepatic breakdown of ATP and also led to decrease excretion of uric acid via kidney. Alcohol consumption also induces hyperlactacidemia, which inhibit uric acid secretion, consumption of bear confers a greater risk of gout than liquor and moderate wine intake does not increase gout risk.27

Pharmacological treatment: Earlier there is a relation found in between hyperuricemia and cardiovascular disease and renal disease so this lead to the evidence that treatment of asymptomatic hyperuricemia started with urate lowering drugs.28

Nowadays asymptomatic hyperuricemia is not treated by pharmacological therapy, that is, with antihyperuricemic agents. Pharmacological treatment is given when—
- Two or more acute gout attacks per year,
- Presence of tophi,
- Stone formation, and
- Those individuals who were taking cytolytic drugs for malignancy in the past.29

Most common drug used for lowering of serum uric acid is allopurinol by blocking uric acid production.

Side effects: Diarrhea, headache, skin rash with itching.

Other toxicities are pyrexia, increase in leukocyte and eosinophil, hypersensitivity syndrome, etc.30,31

Oxypurinol is a metabolite of allopurinol, which is used as an alternative for allopurinol. It is used when severe adverse effects of allopurinol occurs.32

Uricosuric drugs: These drugs are named as probenecid and sulfinpyrazone. They have less side effects stilt use is very limited.33 These drugs decrease the serum uric acid level by uricosuric effect so also increase uric acid in urine and increase the chance of development of uric acid stones.34

Thus, for better effect of these uricosuric drugs, kidney function should be normal, that is, creatinine clearance should be more than 55–60 mL/min and also patient should take at least 2 liters of fluid everyday with no history of nephrolithiasis.

- Symptomatic Hyperuricemia is treated with antihyperuricemic drugs. Basic aim of giving urate lowering agent is to decrease the total uric acid pool and serum uric acid should be below 6.5 mg/dL. Symptomatic hyperuricemia can present as—
  - Acute gouty arthritis
  - Nephrolithiasis
  - Uric acid nephropathy

A. Acute gouty arthritis: Risk of gouty arthritis in those who are hyperuricemic individuals with high level of urate. Usually hyperuricemic person does not develop gout, and there is no need of prophylactic treatment. Also there is no structural kidney damage and no tophi are identifiable before first attack of gout.

Urate lowering agents should be started in those who are not managed by low purine diet, high fluid intake, moderation of alcohol intake, decrease in body weight and not on diuretics, etc.

Hypouricemic therapy started or not decision depends on—
- The number of acute attacks of gout
- More than 9.0 mg/dL of serum uric acid
- Nephrolithiasis
- Uricosuric agents like—
  - Probenecid are used when kidney function is normal, that is, when 24-hour urine sample contains uric acid less than 600 mg (underexcrete) and also need large amount of fluid intake, that is, about 1.5 liter of water intake per day. Starting dose of probenecid is 250 mg bid daily and maximum can be given up to 3 gm/day.
  - Other uricosuric agent like benzbromarone is more effective in CKD patients.
  - Some other agents which are not a hypouricemic drug but have little uricosuric effect are losartan, fenofibrate, and amlodipine are also use.
- Dose of xanthine oxidase inhibitor, allopurinol, is usually start with 100 mg once daily in morning and if required then can be reach maximum up to 800 mg daily morning.

Dose reduction is required for allopurinol in chronic kidney disease patients on the basis of serum creatinine level.
Allopurinol toxicity is more when—
- Patient on thiazide diuretic
- Patient allergic to penicillin and ampicillin
- In Asian who expressing HLA-B 5801

- Febuxostat is approved in the United States and dose is 40 or 80 mg once a day and this drug also needs adjustment in mild to moderate renal disease.
- If patients cannot tolerate or fail to take full dose of above mentioned treatment then another drug is available named as pegloticase, which is a pegylated uricase. This drug is very potent given as 8 mg in every 2 weeks via intravenous route and reduces serum uric acid level very fast.
- Along with hypouricemic drugs an anti-inflammatory drug, that is, colchicine is also given.
  The prophylactic dose of colchicine is 0.6 mg once daily or bid and stops when—
  - Patients serum uric acid level is normal
  - No gout attack up to 6 months
  - As long as tophi present

B. Nephrolithiasis: Antihyperuricemic therapy is recommended for the individual who has both gouty arthritis and either uric acid or calcium-containing stones, both of which may occur in association with hyperuric aciduria. Regardless of the nature of the calculi, fluid ingestion should be sufficient to produce a daily urine volume 2 L.

  Active metabolite of allopurinol, that is, oxypurinol has a long half-life (18 hours) so given as single daily dose. Allopurinol is also useful in patients of gout and those with hyperuricemia or hyperuric aciduria without gout having recurrent calcium oxalate stones.

  Potassium citrate (30–80 mmol/day orally in divided doses) is an alternative therapy for patients with uric acid stones alone or mixed calcium/uric acid stones.

  Allopurinol is also used when 2,8-dihydroxyadenine kidney stones are present.

C. Uric acid nephropathy: This condition is a rapidly worsening of kidney function seen when hyperuric aciduria occurs. In this condition deposition of uric acid crystals occurs in the renal interstitium and tubules leading to partial or complete obstruction of collecting ducts, etc.

For prevention of this condition, allopurinol or rasburicase is given prior to treatment with cytotoxic drugs.

For prevention of deposition of uric acid crystals, iv hydration and diuretics like furosemide given and maintain flow of urine above 100 mL/hour.

Acetazolamide and sodium bicarbonate for urine alkalanization and solubilization of uric acid in urine. During this ensure that pH remains 7.0 and no volume overload.

In addition to this hemodialysis may be required.

Urate oxidase (rasburicase) can also be administered IV to prevent or to treat tumorlysis syndrome.

Conclusion

Hyperuricemia is a purine metabolism disorder, asymptomatic condition usually does not require treatment while symptomatic individuals with or without complications may require urate lowering agent therapy.

References
Abstract

Gout, the most common form of crystal induced inflammatory arthritis, has developed flares due to some modifiable and non-modifiable risk factors. Male sex, increasing age, specific race, and ethnicity with some genetic preponderance are the non-modifiable risk factors. Alcohol, mutton, seafish with other purine rich foods in diet, diuretics, antitubercular medicines, etc. in drugs, chronic kidney disease, diabetes mellitus, hypertension, obesity, dyslipidemia, cardiovascular disease etc in comorbidities are modifiable risk factors. Lifestyle modification, dietary habits, and urate lowering therapy with patient education are important to prevent gout flare.

Introduction

Gout is the most common form of crystal induced inflammatory arthritis, mostly affecting the men. The clinical stages of gout are asymptomatic hyperuricemia, recurrent flares of inflammatory arthritis (gout flare), intercritical gout, chronic gouty arthritis, and tophus formation.

When there is super-saturation of serum uric acid concentration (i.e., ≥6.8 mg/dL in physiological pH and temperature), the monosodium urate (MSU) crystals are deposited in joints and subcutaneous tissues, which lead to acute inflammation and pain. Upon deposition of MSU in human fibroblast-like synoviocytes (FLS), it releases reactive oxygen species (ROS) and reactive nitrogen species (RNS), which lead to FLS necroapoptosis. MSU also can directly cause cytotoxicity and inflammation resulting necroapoptosis of synovium and is mediated by the receptor-interacting protein RIPK-1, RIPK-3, and the pseudokinase mixed-lineage kinase domain-like (MLKL)-driven necroapoptosis pathways. It is said that this necrosis is the primary event of crystal-induced necroinflammation. On the other side, MSU also involve caspase-1-activating NALP3 inflammasome, and produce active interleukin (IL)-1β and IL-18, the proinflammatory cytokines, which lead to influx and activation of neutrophils. Activated neutrophils recruit and activate macrophages to release proinflammatory cytokines like IL-1, IL-6, IL-8, TNF-α, (COX)-2, and LTB-4 at the same time degranulation or lysis of cell membrane of the activated neutrophils results release of inflammatory mediators. The resolution of gout flare occurs due to increase concentration of negative regulatory factors of the inflammation which is initiated by aggregation of neutrophil extracellular trap structures (NETs) and also there is dissolution of MSU or protein coating of MSU crystals, which leads to turning off the ongoing inflammatory process.

In the pathogenesis of gout there have a number of key regulatory points (Flowchart 1). At some of these points therapeutic interventions or risk factors elimination may retard the development of gout or prevent flare (Fig. 1).

Risk Factors

Risk factors for gout flares can be subdivided by non-modifiable and modifiable risk factors (Table 1).
CHAPTER 80
Risk Factors for Gout Flare

Flowchart 1: Key points of pathogenesis of gout

Non-modifiable Risk Factors

Sex
In below 65 age group people, male to female prevalence ratio is 4:1, but above 65 age group people this ratio reduced to 3:1. Mean age of onset in males is about 10 years younger than the females. This may be attributed to enhancement of renal tubular urate clearance in premenopausal women partly due to decrease post-translational expression of urate transporter 1 (URAT1), glucose transporter 9 (GLUT9), sodium-coupled monocarboxylate transporter 1 (SMCT1), and urate efflux transporter ABCG2 by the estrogen and progesterone resulting decreased reabsorption of urate from renal tubules. Male gender has higher numbers of gout flare than females. The risk of incident gout was seen to be higher among the postmenopausal women but the women with surgical menopause or premature menopause (age <45 years) have higher incidence than to those with natural and average age of menopause. In postmenopausal women there is increased incidence of insulin resistance, which can reduce the urate excretion, and therefore hyperuricemia is more common in them than the premenopausal.

Age
The risk of hyperuricemia is strongly associated with increasing age. The chronic illness like diabetes, hypertension, cardiac diseases, renal diseases, etc. are more common in older age and also increases use of
diuretics are another reason for increased prevalence of hyperuricemia. The incidence of first flare is constant across the all age group and in female the incidence of first flare is more in older age group. Over all lower number of flare has been seen in older age group in a large population-based study in the UK.  

**Race/Ethnicity**

Study revealed African Americans had increased risk of gout than the Caucasian and the incidence rate were 3.11 and 1.82 respectively per 1,000 person-years, may be attributed to genetic predisposition with increased incidence of hypertension and use of diuretics in African Americans. In another study over the 20 years of follow-up, African American and Caucasian males had equal risk of incident hyperuricemia (HR 1.12, 95% CI, 0.88-1.40), whereas African American females had 2.3 times higher risk of hyperuricemia (95% CI, 1.34-3.99) than the Caucasian females. Prevalence of hyperuricemia is more in the Māori population than the Europeans (27.1% vs. 9.4% in males and 26.6% vs. 10.5% in females, respectively) in New Zealand. This high prevalence is due to genetic predisposition with high prevalence of comorbidities like obesity, diabetes, hypertension in the background of genetic predisposition. In Southern China, higher prevalence of gout seen in the Minnesota Hmong males (6.1%) than the non Hmong males (2.5%). Age of onset of gout in Hmong males also have significantly younger than the Caucasians (37.4 vs. 55 years).  

**Genetics**

A study involving twins has found that gout is strongly heritable where 90% of the variation in gout concordance attributable to genetic factors. A similar approach revealed that 60% heritability of renal urate clearance and 87% heritability of the fractional excretion of urate. Recently the genome-wide association scanning (GWAS), a human genome project has enabled us to find out the genetic basis of hyperuricemia and gout to some extent. It is evident that the primary cause of gout in 90% of patients is renal under-excretion while renal excretion of uric acid is heritable. So the genetic variation in urate transporter plays a significant role to control serum urate level. The first reported association of the SLC2A9 gene with serum urate concentrations in Italian cohorts was utilized in the Framingham and Rotterdam Heart Studies. Up to 5% variation of serum urate concentration in Caucasians has been explained by genetic variation of the SLC2A9 gene. This variation also influences the risk of gout in Caucasians with odds ratio between 1.3 and 2.2. The said variants also become an extremely significant risk for gout in Māori of New Zealand and Pacific Island with a 500% increased risk (OR=5), and >98% of Māori and Pacific Island patients homozygous for the risk allele compared with 79% of NZ Caucasian patients.

SLC2A9 gene encodes glucose transporter type 9 (GLUT9), which is responsible for reabsorption of a large portion of urate. So mutation of SLC2A9 can be suspected in patient of hypouricemia without mutation of other genes like SLC22A12. There are number of studies which have correlated polymorphisms in SLC2A9 with uric acid levels and gout.

SLC22A12 encodes urate anion transporter 1 (URAT1), which is seen in the brush border of proximal tubules and also have significant role for reabsorption of urate. It was first identified in a Japanese patient having hypouricemia and the said gene was found to be mutated. Polymorphism has also been seen in SLC22A12.

ABCG2 encodes the adenosine triphosphate (ATP)-binding cassette transporter 2 (ABCG2), which mediates urate secretion across the apical membrane of proximal tubules. The variants were indentified through GWAS and mutation of it can cause hyperuricemia.

**Modifiable Risk Factors**

**Dietary Factors**

**Alcohol:** We all know that consumption of ethanol beverages, especially beer, is significantly associated with higher risk of incident gout. In few study, wine appears to protective against gout flare but Tuhina Neogi et al. (2014), concluded that the episodic alcohol consumption, regardless of type of alcoholic beverage, was associated with higher risk of gout flares. Beer contains significant amount of guanosine, which is most readily absorbed purine, responsible for high urate production. A study to compare increase of serum uric acid level between alcoholic beer to nonalcoholic beer revealed that plasma uric acid levels had increased 6.5% and 4.4% (p<0.05), respectively points out that purine load alone had a significant effect on uric acid level. Ethanol increases uric acid production by increasing ATP degradation to uric acid precursors. It also causes lactic academia, which results in decrease urate excretion.
**Purine-rich foods:** Uric acid is the end product of purine degradation. Intake of purine rich foods such as meat or sea food is associated with hyperuricemia and incident gout.8 Choi et al. found in their study that the differences in uric acid levels between the extreme quintiles of intake were 0.48 mg/dL for total meat (95% confidence interval [95% CI] 0.34, 0.61; P < 0.001 for trend), 0.16 mg/dL for seafood (95% CI 0.06, 0.27; P = 0.005 for trend), after adjusting for age.10 Yuqing Zhang and his colleagues proved that 2 days intake of highest quintile of purine, mainly from animal source increases the risk of flare almost five times than the lowest quintile of purine and the association was independent of other risk factors like sex, alcohol consumption, diuretics or allopurinol use. Long-term moderate amount of purine rich vegetables (like—lentils, spinach, mushrooms, peas, and cauliflower) intake are not associated with gout flare.10 Although soy has moderate purine content, it also not been shown to be associated with gout rather it may be inversely associated with hyperuricemia.

**Soft drinks, fructose consumption:** In first step of fructose metabolism there is phosphorylation by ATP, which accelerates purine catabolism and de-novo purine synthesis. Fructose may increase the risk of insulin resistance which can cause reduction of renal excretion of urate and leads to hyperuricemia. Sugar sweetened soft drinks and fruit juices contain high concentration of fructose, the intake of which is associated with high level of serum urate and may be an important risk factor for frequent gout flare. NHANES, a cross-sectional study showed increased in urate of 0.33 mg/dL (95% CI, 0.11-0.73) in participants drinking 1-3.9 sugar-sweetened servings per day than those drinking none after adjustment for diet including total energy intake, age, sex, medications, hypertension, and glomerular filtration rate. Men who ingested the highest 5th of fructose incurred double the risk of gout than those in the lowest (RR 2.02, 95% CI, 1.49-2.75) after adjustment for intake of total carbohydrate.11

**Dairy products:** Increased amount of dairy products intake is associated with decreased level of urate and incident gout. It has been shown in a study that the glycomacropeptide (GMP), a milk fragment and G600 milk fat extract have anti-inflammatory effects and they acts by decreasing interleukin-1β (IL-1β) expression, which may be the second protective role of dairy product.

**Vitamin C:** Vitamin C has a protective role against gout. It increases renal clearance of urate by increasing fractional excretion of uric acid. Vitamin C competitively inhibits the urate reabsorption in proximal tubules. In an RCT where significant reduction of serum uric acid levels was seen with supplementation of 500 mg/day of vitamin C and the mean uric acid reduction was 0.5 mg/dL (95% CI, -0.6 to -0.3).12

**Cherry:** In a case-cross over study, consumption of cherry was found to lower recurrent gout attacks by 35%. This beneficial effect of cherry may be due to its effects on glomerular filtration and probable inhibition of xanthine oxidase along with having its antioxidant properties.

**Drugs**

**Diuretics:** Diuretics can cause hyperuricemia by increasing uric acid reabsorption in the proximal tubules, increasing secretion of uric acid and contraction of plasma volume. Increased level of urate usually seen few days after initiation of diuretics and the association is dose dependent, and the concentration persists for prolonged period of administration. Hunter et al. (2006) pointed out that recent use of diuretics is associated with a significantly higher risk for gout flare.

**Anti-tubercular drugs:** Pyrazinamide can cause more than 80% reduction in renal excretion of uric acid at 300 mg therapeutic daily dose and precipitate gouty attack. The active metabolite of pyrazinamide has a trans-stimulatory effect on URAT1, a member of the organic anion transporter (OAT) family, resulting reabsorption of urate from renal tubules. So patient having first attack of gout should monitor the uric acid level and needs prompt discontinuation of the drug on recurrent gout flare. Another drug, Ethambutol, can also increase SUA and precipitate the attack.

**Immunosuppressive agents:** Cyclosporine use in an organ transplant recipient is most important predictors of incident gout and gout flare. Recently Tacrolimus also to be seen associated with hyperuricemia and gout flare but relatively less in frequency may be due to impairment of renal functions which is seen more frequently in cyclosporine use.

**Aspirin:** Studies shows that low dose aspirin can cause hyperuricemia but in contrast high dose aspirin is shown to have uricosuric effect. This paradoxical effect is due to fact that low dose of aspirin acts as facilitator of urate reabsorption and high dose acts as inhibitor of urate reabsorption through Renal Urate Transporter (URAT1).13
So intake of low dose aspirin can causes acute or recurrent gout flare and acts as an important risk factor.

**Comorbidities**

Hyperuricemia is commonly seen in chronic kidney disease (CKD) and is frequently associated with incident gout and recurrent gout flare, which requires adequate ULT. Hyperuricemia in CKD is due to decreased urinary clearance of uric acid. Approximately two-thirds of uric acid is excreted through kidney and is severely impaired in depressed renal function. Obesity shows to a strong risk factor for incident gout and flare in those having previous attack. Hypertension is consistently seems to be another risk factor for flare up especially with diuretic use. It is concluded in various studies that in hypertension and cardiovascular disease there is increased xanthine oxidase activity and high serum urate level. Diabetes is an independent risk factor. Suppiah et al. (2008) demonstrated that gout is highly prevalent in patients with type 2 diabetes and highest (41%) in men over the age of 65 years and requires early recognition and management. Hypertriglyceridemia and hypercholesterolemia both are associated with gout flare.

**Other Risk Factors**

**Immunization** is a pro-inflammatory trigger, which can also acts as a trigger for gout flare. An internet-based case-crossover study showed that immunization doubled the risk of a gout flare within the ensuing 48 hours of vaccination compared with periods in not vaccinated people (odds ratio [OR] 1.99, 95% CI 1.01-3.89).9

There is an increased incidence of gout flare in post-surgical periods. Study shows patient having a previous history of gout who undergoes laparoscopic gastric bypass surgery can frequently develop gout flare. Increase release of fat, starvation, volume contraction may all responsible for high serum urate levels in post-surgical periods.

**Initiation of urate lowering therapy (ULT)** may precipitate a gout flare, especially in early months but in long-term use it cannot prevent or reduce the frequency of flare. So adequate anti-inflammatory prophylaxis overlap for some duration may sometimes be needed while initiating ULT.

**Intake of coffee** is protective for gout flare. It increases renal blood flow, and hence increases urate excretion. Again it may increases the insulin sensitivity, which has a positive role for urate clearance.

**Conclusion**

Gout flare is very much common and a large number of patients of incident gout develop at least one flare in their lifetime. The predisposing factors for gout flares act on various points of its pathogenesis. Few factors have protective effect also. For prevention of gout flares daily consumption of alcohol must be reduced or stopped, composition of diet is to be changed, dietary supplement like Vit. C, cherries is to be given, ideal body weight must be maintained, comorbidities should adequately be managed and anti-inflammatory prophylaxis may be needed in early months of initiation of ULT in an incident gout patient. Moreover, patient’s education is important for proper lifestyle modification and pharmacological therapy other than ULT in gout patients with comorbidities.

**References**

Abstract

Healthy bone is dependent on interplay between vitamin D, calcium, and phosphates. In addition to its important role in maintaining bone health, a new area of vitamin D’s role in pleiotropic activities unrelated to skeletal metabolism is now recognized and it is now increasingly being clear that optimum levels of vitamin D is also important in preventing several other dreaded chronic diseases including DM, CVD, and malignant diseases. Osteoporosis and fractures are common in elderly population and one of the most important causative agents is hypovitaminosis D. Hypovitaminosis D prevalence in India is widespread. Correction of vitamin D deficiency improves skeletal health and prevents rickets in younger population, osteoporosis, and fractures in elderly population. There are plethora of research suggesting the extra-skeletal benefits of vitamin D.

Introduction

Healthy bone is dependent on interplay between vitamin D, calcium, and phosphates. Vitamin D facilitates absorption of calcium from gut and plays a major role in calcium and phosphate balance in the body.

The major source (90%) of its availability is through dermal synthesis in the presence of Sunlight. Vitamin D is also ingested in the diet as vitamin D2 (ergocalciferol), mainly from some plants and UV irradiated yeast & mushroom and vitamin D3 (cholecalciferol) from animals (oily fish and fish liver oils).

Its deficiency accelerates bone turnover and bone loss leading to rickets in children, where the cartilage is not formed, osteomalacia, where the newly formed bone matrix (osteoid) is not mineralized and osteoporosis, the latter causing falls and fractures in elderly people. In addition to its important role in bone health, it also has some role in preventing several other dreaded chronic diseases including diabetes mellitus (DM), cardiovascular disease (CVD), and malignant diseases.

Metabolism

The precursor of vitamin D, 7-dehydrocholesterol, present in the epidermis and dermis, is converted nonenzymatically to pre-vitamin D3 during exposure to solar rays (UV-B radiation of wavelength 290–320 nm). At body temperature this undergoes rearrangement of its structure and gets converted to vitamin D3. Vitamin D3 from the skin or vitamin D2 from plant sources is biologically inactive. They enter the circulation bound to vitamin D binding protein (DBP) and reach liver and get converted enzymatically to 25(OH) vitamin D. The crucial active vitamin D1, 25-dihydroxyvitamin D or calcitriol is synthesized here. Both serum calcium and phosphorous as well as serum parathormone (PTH) have important role in regulating its synthesis in kidneys. As serum calcium and phosphate levels rise the production of 1,25(OH)2D falls. Vitamin D level in turn regulates its own synthesis. As its level becomes optimal the synthesis of PTH decreases. From the kidneys 1,25(OH)2D reaches intestine and bone
where its major action in increasing calcium absorption from the gut happens. Also, through osteoclastic activity in bone, calcium and phosphorous are drawn out. All these help in maintaining serum calcium and phosphorous levels. Vitamin D receptor (VDR) presents in these tissues helps in this action. VDR acts in the nuclei of vitamin D target cells to regulate the expression of genes whose products control diverse, cell type–specific biological functions. $1,25(OH)_2 D$ stimulates the absorption of calcium in the duodenum and increases calcium influx in distal tubules of kidney through nuclear VDR; latter action is specifically regulated by PTH level. It also stimulates intestinal phosphate absorption, directly suppresses PTH release from the parathyroid gland, regulate osteoblast function. It allows PTH-induced osteoclast activation and bone resorption.

**Normal Value of Vitamin D and Defining Hypovitaminosis**

Though brief casual solar exposure is equivalent to ingestion of 200 IU/day, this depends on variables like the skin type, latitude, season, time of day, atmospheric pollution, solar zenith angle, and melanin pigmentation. The solar zenith angle is more oblique in winter season and during early morning and late afternoon. Before 10 am and after 3 pm the UV-B rays penetrating the earth is at minimum levels and Vitamin D synthesis through skin layers is negligible during this time period. Prolonged UV-B radiation converts pre-D3 to lumisterol and tachysterol, its inactive metabolites, protecting the body from vitamin D toxicity.

As $25(OH)D$ levels rise serum PTH falls. Once vitamin D level reaches 40 ng/mL PTH level stops rising further. Intestinal absorption of calcium increases from 45% to 65% when vitamin D level increases from 20 ng/mL to 32 ng/mL in women. Currently serum total ($25[OH]D$) concentration (sum of 25-hydroxyvitamin D$_3$ and D$_2$) is considered the best biomarker to define vitamin D status. It has a long half-life of 2–3 weeks. Its deficiency leads to rickets and osteomalacia and with adequate intake of vitamin D both these diseases disappear with increase in vitamin D levels. A level below 12 ng/mL usually causes rickets and osteomalacia. For a healthy bone, levels between 20 ng/mL and 50 ng/mL is required.

Biochemically, a deficient state is defined when $25(OH)D$ levels are less than 20 ng/mL and an insufficient state when levels hover between 20 ng/mL and 29 ng/mL. ICMR/FSSAI’s recommendation on RDA of vitamin D is 400 IU—all age groups. Other scientific organizations have developed RDA basing upon age to 400–800 IU.

**Magnitude of Hypovitaminosis D in India**

Hypovitaminosis D prevalence in India is widespread. Community-based studies report a prevalence varying from 56% to 93% indicating widespread prevalence in both sexes and all age groups. Most of these studies have taken a cut off value of $25(OH)D$ as less than 20 ng/mL.

**Vitamin D Deficiency and Its Effects on Skeletal Health**

A vitamin D deficient patient is able to absorb only 10–15% of dietary calcium and about 60% of dietary phosphorus. Hypophosphatemia and hypocalcemia are a consequence. Persistent vitamin D deficiency leads to secondary hyperparathyroidism. This in turn causes increased synthesis and secretion of PTH. By increasing calcium absorption from kidneys PTH keeps calcium levels at near normal levels. It also stimulates osteoclastic activity. The net result is, though the serum calcium level increases but the casualty is bone matrix which becomes weak and osteopenia and osteoporosis sets in. Hip fracture is an unfortunate consequence of secondary hyperparathyroidism. Chronic severe vitamin D deficiency results in bone demineralization causing osteomalacia in adults and rickets in children. This also leads to increased bone pain. So, Vitamin D is a bridge between a healthy bone and calcium-phosphorus balance in the body.

**Non-calcemic Functions of Vitamin D**

For the last several decades scientists are trying to ascertain if there is a role of vitamin D in preventing various chronic metabolic, cardiovascular, autoimmune, and neoplastic diseases. They have detected the presence of VDR in almost all cells and tissues in the body including
neurons in the brain, gut, breast tissue, immune cells and several other cells. It has been shown that the conversion of 25(OH)D to 1,25(OH)2D is possible in many tissues and cells besides kidneys. This realization has opened a new area of vitamin D’s role in pleiotropic activities unrelated to skeletal metabolism. This active form of vitamin D gets metabolized into calcitroic acid and become inert locally and does not reach the circulation to act on skeletal metabolism. Only 1,25(OH)2D, which is produced in kidneys can be exported to the blood stream. This locally produced active form of vitamin D influences several genes which prevent proliferation of cells and can cause apoptosis too.

Cancer

Studies have shown at least 14 cancers, including colorectal, breast, and prostate are related to vitamin D deficiency.13-15

Serum vitamin D level ≥33 ng/mL, compared to ≤12 ng/mL was associated with 50% lower risk of colorectal cancer.16

WHO working group has found link between increased risk of colorectal cancer with low serum vitamin D levels.17

A meta-analysis of prospective studies has shown that the risk of cancer breast decreased with vitamin D levels between 27 and <35 ng/mL with flattening of effects above 35 ng/mL in postmenopausal women.18

Several studies have underlined the fact that countries which are at a distance far away from equator have more risks of suffering from certain cancers. This may be because of less sun exposure and decreased UV radiation causing less vitamin D synthesis in higher altitudes.19-22

Several observational studies and a few RCTs23-25 have shown that high normal vitamin D levels are linked to decreased incidence of several malignancies including colorectal, breast, prostate, etc. Some have also shown decreased mortality rates due to cancer.25

Immune System

VDR and vitamin D metabolic enzymes are present in almost all cells of innate and adaptive arms of immune system including dendritic cells, B and T cells, and macrophages. Researchers have found that all these cells produce active vitamin D without calcium homeostatic regulation.26

Researchers have found that vitamin D reduces activation of acquired immune system whereas it activates the innate immune system particularly monocytes and macrophages.

Multiple sclerosis in north and south hemisphere, T1DM and RA in north hemisphere are found in increasing numbers at higher altitudes where UVR is less. Studies have shown that UVR downregulates cellular immunity by attenuating T helper T cell mediated immune responses. UVR thus might be beneficial in MS, T1DM, and RA. One of the possible mechanisms for downregulation involves UVR induced vitamin D synthesis. Thus, vitamin D may have a protective role in preventing T1DM.27

Observational studies have found a strong link between prevalence of MS and less than normal vitamin D levels.28,29

Risk for developing active TB and its link to low levels of vitamin D has been found in one meta-analysis,30 whereas vitamin D supplementation can enhance rapid clearance of sputum in active TB;31 it can also protect against respiratory infections.32

In conclusion, a link between vitamin D endocrine system and immune system is highly plausible, but whether its deficiency has real implications for infections or autoimmune diseases is yet to be confirmed by large scale RCTs.33

Cardiovascular Diseases

Several genes playing important roles in CV system are targets of vitamin D signaling, including those encoding renin, PAI, and thrombomodulin.

Conclusion from a meta-analysis of 19 prospective studies is that risk of CVD is inversely associated with vitamin D levels of 8–24 ng/mL.34 Similar conclusion is derived from another meta-analysis of 34 publications related to vitamin D levels and CVD events and mortality.35 In contrast, VIDA trial did not support such an association.36

In northern hemisphere as one goes from south to north the incidence of hypertension increases. One reason could be reduction of solar induced vitamin D synthesis. Animal studies have shown VDR null mice develop high renin hypertension.37 Some studies support inverse relationship of BP and vitamin D levels38 whereas others do not.39
Vitamin D and Skin
Keratinocytes express all enzymes of vitamin D metabolic pathway and skin can synthesize its active form in presence of solar UV-B rays. Active vitamin D produced locally controls keratinocyte proliferation and differentiation as well as epidermal barrier integrity. Topical application of vitamin D analogues reduces the symptoms of psoriasis, probably due to its anti-inflammatory properties and effects on epidermal cell proliferation.

The same wave lengths of UV-B solar rays, which are required for dermal synthesis of vitamin D, are also oncogenic. It is therefore a difficult choice to make how much of solar rays one must be exposed to while avoiding long-term risk of developing skin cancer.36

Vitamin D and Muscle Weakness
Muscle strength correlates positively with vitamin D levels in elderly male patients.39

Proximal muscle strength may modestly improve with vitamin D supplementation given to elderly subjects with vitamin D levels <12 ng/mL.41

Some studies have found no effect on reducing risk of falls with vitamin D supplementation.

Overall, the data suggests vitamin D supplementation in elderly vitamin D deficient subjects may modestly improve muscle function, improve balance, and decrease the risk of falling.33

Type 2 DM
The risk of developing T2DM is reduced with higher vitamin D levels.43

Mortality
A recent meta-analysis of observational studies and RCTs which reported associations between vitamin D and cause specific mortality outcomes has concluded that there is inverse relationship between vitamin D levels and risk of death due to CV disease, cancer, and other causes and also vitamin D supplementation significantly reduces overall mortality among older adults.44

Treatment of Vitamin D Deficiency
The usual adult dose for treatment of vitamin D deficiency is 60 K IU of vitamin D3/week given for 8–12 weeks followed by maintenance dose of 60 K IU once every month.

Conclusion
Vitamin D deficiency is quite prevalent in India. It is now recognized as an important health problem, which needs to be addressed by stakeholders. Vitamin D deficiency and skeletal consequences are well known. There is significant improvement in rickets when treated with vitamin D supplements. Though several researchers have pointed out the relationship between vitamin D status and non-skeletal diseases, more research is required to conclusively prove the link.

References
Hyponatremia—An Update on Diagnosis and Treatment

Samir Sahu

Abstract

Hyponatremia, defined as serum sodium concentration of less than 135 mEq/L, is a common electrolyte disorder that often poses a diagnostic and a therapeutic challenge. The primary aim of the diagnosis is to differentiate between acute (<48 hours) versus chronic (>48 hours), symptomatic versus asymptomatic and hypotonic versus non-hypotonic hyponatremia. Further, hypotonic hyponatremia is differentiated on the basis of volume status, urine sodium, and urine osmolality. The treatment for hyponatremia is decided on the basis of duration and symptoms. For acute symptomatic hyponatremia and severe chronic hyponatremia, bolus of 3% hypertonic saline is the initial treatment of choice. Though the first-line therapy for most forms of chronic hyponatremia is fluid restriction, therapy to increase renal-free water excretion like vasopressin receptor antagonists, loop diuretics, and urea are often necessary.

Introduction

Hyponatremia is a common electrolyte disorder, defined as sodium concentration below 135 mEq/L.¹ It is a state of relative water excess to sodium. With the expanding use of various medications and the growing elderly population, the incidence is on a rising trend. Among the inpatients, especially in ICUs, the incidence is up-gear to 15–30%.² Consequences will be catastrophic, if not treated with prompt measures. Hence, a well-directed investigation from the gamut of tests available helps in quick and accurate diagnosis. Incorporating the recent concepts in the management reduces the morbidity and mortality.

Definition and Background

Plasma Osmolality ($P_{\text{osm}}$): It's the ratio between plasma solutes and water. The major contribution of plasma solutes is provided by sodium salts while rest by other ions (e.g., potassium), glucose, and urea.

Urine Sodium ($U_{\text{Na}}$): Urine sodium is a measurement of the concentration of sodium in the urine. On spot estimation, the values are normally more than 20 mEq/L.

Urine Osmolality ($U_{\text{osm}}$): Urine osmolality is the measure of number of dissolved particles per unit of water in the urine. Urine osmolality in an individual with a normal diet and normal fluid intake ranges 500–850 mosm/kg water.

Osmotic Demyelination Syndrome (ODS): A dreaded disorder characterized by the wide spread development of demyelination in the pontine as well as the extrapontine regions usually because of rapid correction of hyponatremia.

Classification and Symptoms of Hyponatremia

See Table 1.
Hyponatremia—An Update on Diagnosis and Treatment

### Evaluation

#### History

A history of electrolyte-rich fluid loss (vomiting, diarrhea, or diuretic therapy) may indicate hypovolemia. Past history of CNS disease, malignancy, HIV infection, and plasma cell dyscrasia may add important clues to the diagnosis. A history of common drugs causing hyponatremia (thiazide diuretics, mannitol, antidepressants, antiepileptics, antipsychotics, and ecstasy) should not be missed.

#### Physical Examination

Peripheral edema and/or ascites may be a manifestation of renal failure, cirrhosis, or heart failure. Look for signs of extracellular volume depletion such as decreased skin turgor, tachycardia, orthostatic or persistent hypotension. Sometimes patient may present with only signs of adrenal insufficiency or hypothyroidism.

#### Investigations

Laboratory testing is almost always essential to establish the diagnosis. Investigations helpful in the initial evaluation of hyponatremia include: complete blood count, serum glucose, urea, creatinine, sodium, potassium, chloride bicarbonate, calcium, lipid profile, and liver function test. U<sub>osm</sub> and U<sub>Na</sub> play an inevitable role in the evaluation of hyponatremia (Flowchart 1).

### Differential Diagnosis

Hyponatremia may be divided into:

- Pseudohyponatremia
- Isotonic or hypertonic hyponatremia
- Hypotonic hyponatremia

In the first two situations, hyponatremia and hypoosmolality are discordant; these are important to recognize, as they represent situations where hyponatremia need not be treated.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Severity</th>
<th>Serum sodium</th>
<th>Duration</th>
<th>Neurological symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>&lt;120 mEq/L</td>
<td>Acute (&lt;48 hours)</td>
<td>Vomiting, seizures, coma, cardiorespiratory distress</td>
</tr>
<tr>
<td>Moderate</td>
<td>120–129 mEq/L</td>
<td>Nausea without vomiting, confusion, headache</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>130–134 mEq/L</td>
<td>Chronic (&gt;48 hours) or duration unknown</td>
<td>Altered mood, concentration and cognitive deficits, gait disturbances, falls</td>
</tr>
</tbody>
</table>

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**Pseudohyponatremia**

Hyperlipidemia, hyperproteinemia, plasma cell dyscrasia.

**Isotonic or Hypertonic Hyponatremia**

Sodium concentration falls by approximately 2 mEq/L for each 100 mg/100 mL rise in glucose concentration. Other causes include mannitol, IVIG, and absorption of glycine or sorbitol, the irrigation solutions during transurethral resection of prostate.

**Hypotonic Hyponatremia**

Most have hypotonic hyponatremia, as serum sodium concentration remains one of the major determinant of tonicity. Evaluation of hypotonic hyponatremia has to be done meticulously (Flowchart 1). Severely reduced glomerular filtration rate (GFR) and intake of thiazide diuretics are important causes of hypotonic hyponatremia.

#### Severely Reduced GFR:

Free water excretion is significantly reduced in advanced renal impairment (e.g., GFR <15 mL/min) leading to hyponatremia.

**Thiazides:** An occasional but a severe complication of thiazide typically begins soon after onset of therapy; but at times occur on long-term therapy. Improvement on discontinuation helps to distinguish from syndrome of inappropriate antidiuretic hormone (SIADH), which also shares similar features.

Those patients, who do not have either of the above, should be evaluated for the evidences of fluid overload. They can be classified as hypervolemia, euvolemia and hypovolemia.

**Hypervolemia**

The major causes of hyponatremia in fluid overload conditions include heart failure (HF) and cirrhosis, typically in advanced stages. In spite of excess plasma and extracellular volumes in the above, the carotid sinus baroreceptors sense a reduced pressure, because
Flowchart 1: Approach to determine the cause of hypotonic hyponatremia

Hypotonic hyponatremia

Impaired GFR (or) thiazides

No

Signs of fluid overload

No

Signs of hypovolemia

No

Urinary sodium and osmolality

Urinary osmolality <100

No

Urinary sodium >40

No

Hypovolemic hyponatremia

Yes

Evaluate for: Glucocorticoid deficiency Hypothyroidism

No

SIADH

Yes

Evaluate for the etiology

Renal failure, thiazide use

Yes

Heart failure, cirrhosis, etc.

Yes

Urine sodium

Low <25 mEq/L

GI losses

25–40 mEq/L

Remeasure after isotonic saline infusion

High >40 mEq/L

Renal losses

Diuretics primary adrenal-insufficiency Cerebral salt wasting
of a fall in cardiac output in heart failure and arterial vasodilatation in cirrhosis.

**Hypovolemia**

Clinical features of hypovolemia are not always diagnostic. It may be either due to a renal fluid loss or an extrarenal fluid loss. Measurements of $U_{\text{Na}}$ and Urine chloride ($U_{\text{Cl}}$) concentrations distinguishes both.\(^5\)

- **Low $U_{\text{Na}}$ (<25 mEq/L):** Seen in patients of gastrointestinal fluid losses (e.g., diarrhea) and in renal fluid loss due to diuretics, if measured after the diuretic effect has abated.

- **High $U_{\text{Na}}$ (>40 mEq/L) with low $U_{\text{Cl}}$ (<25 mEq/L):** Seen among hypovolemic hyponatremic patients with metabolic alkalosis caused secondary to vomiting.

- **High $U_{\text{Na}}$ and $U_{\text{Cl}}$ concentration (>40 mEq/L):** Commonly seen during diuretic therapy with its effect still on. Other causes of renal fluid loss with hyponatremia are primary adrenal insufficiency and cerebral salt wasting syndrome (CSW). Clinical features of hypovolemia differentiates CSW from SIADH.\(^6\)

**Euvolemia**

- **Low $U_{\text{Na}}$ (<25 mEq/L) with Low $U_{\text{osm}}$ (<100 mosmol/kg):**
  - **Primary polydipsia:** It is usually seen in psychiatric patients. It may cause hyponatremia when water intake is so high that it exceeds the normal excretory capacity in spite of it being normal. Once water intake stops, the serum sodium concentration will increase spontaneously.
  - **Malnutrition:** It occurs in beer drinkers (beer potomania) or in those on a low-protein, high-water diet, in which dietary solute intake (sodium, potassium, protein), and therefore solute excretion is so low that the rate of water excretion is markedly diminished even though urinary dilution is intact.

- **High $U_{\text{Na}}$ (>40 mEq/L) and $U_{\text{osm}}$ (>300 mosmol/kg):**
  - **SIADH:** The most common cause of hyponatremia in euvolemic patients is a diagnosis of exclusion. The patient may also have other corroborative features like hypouricemia (<4 mg/dL), and low blood urea nitrogen (<5 mg/dL). The underlying mechanism is presumed to be due to increased clearance of uric acid and urea respectively, as a result of water retention and volume expansion in the SIADH and stimulation of V1a receptor via an uncertain mechanism.\(^7\) Administration of normal saline worsens the hyponatremia.
  - **Reset osmostat:** They present similar to SIADH, with a moderately reduced plasma sodium concentration (usually between 125 and 135 mEq/L), that is stable on multiple measurements.
  - **Severe hypothyroidism:** Causes hyponatremia via uncertain mechanisms.
  - **Cortisol deficiency:** Secondary adrenal insufficiency (hypopituitarism), in contrast to primary adrenal insufficiency, presents with euvolemic hyponatremia and biochemical features similar to SIADH. The mechanism is found to be due to the interruption of negative feedback loop of cortisol on antidiuretic hormone (ADH) secretion and hypersecretion of ADH as a result of reductions in systemic blood pressure and cardiac output.\(^1\)

**Treatment**

**Aims of Therapy**

- **Prevention of further fall in serum sodium:** The patients prone to develop are self-induced water intoxication and parenteral fluid administration.

- **Prevent brain herniation:** The vulnerable are, patients with acute hyponatremia and associated intracranial pathology.

- **Relieve symptoms of hyponatremia:** Even the most severe symptoms can be relieved by a correction of sodium levels by 4–6 mEq/L during the first 24 hours.

- **Avoid over correction:** Rapid correction of chronic hyponatremia may lead to ODS.\(^1\) To avoid this, the maximum rate of correction should be 8 mEq/L in any 24-hour period. The risk factor of ODS are mentioned in Table 2.

**Indications for Hospitalization**

- **Acute hyponatremia**
- **Symptomatic hyponatremia**
- **Severe hyponatremia**

**Acute Symptomatic Hyponatremia (or Chronic with Severe Symptoms)**

Severe symptoms are reflective of brain edema, small increase in serum sodium concentration may be sufficient
enough to improve edema and prevent herniation; failing, death may follow rapidly. Since there is no brain adaption with acute hyponatremia, chances of ODS is little.

Intravenous (IV) infusion of 150 mL, 3% saline over 20 minutes to achieve a target of 4–6 mEq/L increase in serum sodium. The same dose shall be repeated with serum sodium monitoring after every infusion. In non-responders, continue infusion with 3% saline aiming at 1 mEq/L/hr increase in serum sodium concentration. Adrogué–Madias equation \[\text{Change in Serum Na} = \frac{(\text{infusate Na} – \text{serum Na})/(\text{tbw}+1)}{}}\] may be used for estimating the correction rate, while serum sodium being monitored 4 hourly. Etiology specific treatment is preferred once the desired levels are attained.

**Acute Asymptomatic Hyponatremia**

Even though the symptoms are not much pronounced, an acute drop in serum sodium to a level more than 10 mEq/L, may worsen the clinical condition. Hence, patients at risk are to be treated with a single IV infusion of 150 mL 3% saline, so as to prevent further drop. Serum sodium to be monitored every 4 hourly, till the cause specific treatment is initiated.

**Chronic Asymptomatic Hyponatremia**

These patients are particularly predisposed to develop ODS from rapid correction. If the hyponatremia is severe (<120 mEq/L), initiate IV infusion of 3% saline at 15–30 mL/hr targeting a maximum correction of 8 mEq/L. After sodium correction in these patients and also in cases of mild to moderate hyponatremia, provide a cause specific treatment.

**Treatment of Specific Hyponatremia**

- **Hypovolemic hyponatremia**: Gastrointestinal losses, vomiting, and diarrhea and renal loss secondary to diuretics are accompanied by hypokalemia, where measures should be taken to correct hypokalemia first rather than hyponatremia. Sodium and potassium being the exchangeable ions, with correction of potassium, sodium levels are restored; however, correcting sodium levels first, risks ODS, due to the rapid correction. Extracellular volume must be restored with IV infusion of 0.9% saline or a balanced crystalloid solution at 0.5–1.0 mL/kg/hr to achieve the desired sodium levels. In primary adrenal insufficiency after the initial measures, fludrocortisone may be added along with hydrocortisone.

- **Euvolemic hyponatremia**: This area remains a challenge in clinical practice. The clinical presentation varies and often has some underlying disease.
  - **SIADH**: Fluid restriction is conventionally considered as the first line of treatment. However, the response to therapy depends on the levels of AVP. Oral salt may be added among patients with serum sodium above 120 mEq/L and very mild or absent symptoms. Loop diuretics shall be used as a concurrent therapy in patients with urine osmolality above 500 mosmol/kg. Urea is considered as an alternative to the combination of loop diuretics and oral salt. It has the advantage over any, as it corrects hyponatremia gradually without risk of over correction. However, poor palatability and azotemia had made its use limited in clinical practice. Vasopressin (V2) receptor antagonists (Vaptans) can be added if adequate response is not noticed. Tolvaptan, an oral V2 receptor antagonist initiated at 15 mg/day, can be gradually titrated by 15 mg/day to a maximum dose of 60 mg/day. The commonly noticed side effects are dry mouth, thirst, increased urinary frequency, dizziness, nausea, and orthostatic hypotension. Although hepatotoxicity was not noticed in the recent studies, early trials had shown elevation of alanine aminotransferase (ALT). Hence, its use should be restricted to 30 days and not to be used in patients with underlying liver diseases. Of utmost importance is liberal fluid intake, especially during first 24–48 hours, since Vaptans clear free water and there are high chances for rapid correction with fluid restriction.

  - Monitor serum sodium concentration 6–8 hourly till 48 hours.

**TABLE 2** Risk factors for ODS

<table>
<thead>
<tr>
<th>Risk factors</th>
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</thead>
<tbody>
<tr>
<td>Serum sodium ≤105</td>
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</tr>
<tr>
<td>Hypokalemia</td>
<td></td>
</tr>
<tr>
<td>Alcoholism</td>
<td></td>
</tr>
<tr>
<td>Malnutrition</td>
<td></td>
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<tr>
<td>Liver disease</td>
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</table>
— **Hypothyroidism**: Thyroxine replacement along with fluid restriction suffice.
— **Glucocorticoid deficiency**: Nearly always responds to glucocorticoid replacement. Prompt water diuresis following initiation of glucocorticoid treatment supports the diagnosis.
— **Primary polydipsia**: Counseling for fluid restriction and alternative methods such as wetting the mouth with ice chips, ameliorates sensation of thirst and helps to reduce fluid intake. Studies had shown favorable role of antipsychotic drugs in reduction of polydipsia and prevention of recurrent hyponatremia.3

- **Hypervolemic hyponatremia**: Hyponatremia in hypervolemic conditions such as liver cirrhosis, HF, and end stage renal failure heralds a poor prognosis. Notwithstanding the cause, the primary treatment rests on sodium and water restriction. Fluid restriction to 50–60% of daily fluid requirement or a gross restriction to daily input of less than 800 mL/day is generally followed. Loop diuretics interferes the counter current mechanism in the thick ascending loop of Henle, giving rise to a state of ADH resistance, resulting in less concentrated urine. Vaptans can be added in HF and liver cirrhosis.

### Treatment of Sodium Overcorrection

In situation where there is over correction of hyponatremia, electrolyte-free water is infused at 10 mL/kg over 1 hour while urine output and fluid balance are strictly monitored. In addition, IV desmopressin 2 μg, not more than 8 hourly, may be considered after expert opinion.8

### Conclusion

The laboratory investigations plays a key role in diagnosis of specific causes of hyponatremia, besides the goal directed history and physical examination. Amongst them, the widely and cheaply available $U_{Na}$ and $U_{osm}$ are the crucial decision-makers. The recent evidence supports bolus infusion of hypertonic saline, for certain serious conditions of hyponatremia. Correction rate should not exceed 8 mEq/L in any 24 hours, irrespective of the duration and severity.

### References

Osteoporosis is common silent disease. Its prevalence increasing due to increase in geriatric population. It is associated with increase in morbidity and mortality in elderly population. Prevention of first fracture and targeting young population for primary prevention is key in successful management of this chronic problem.

Introduction
With the increase in the life expectancy, the geriatric population is rising worldwide; therein increasing the cascade of "Non-infectious chronic diseases". Amongst them, osteoporosis being a silent killer is one of the important causes of mortality and disability.

Osteoporosis is defined as low bone mineral density (BMD) caused by altered bone strength ultimately predisposing patients to low impact fragility fractures. Strength of bone is assessed by its mass and quality. Osteoporosis is a process that develops gradually over many years as we age.

Incidence
Decrease bone strength and fragility fractures are common worldwide. It is estimated that around 13–18% of women above 50 years of age are osteoporotic. Fracture risk in these women is around 40% in the remaining life. In a longitudinal study in USA on 200,000 asymptomatic women above 50 years without known osteoporosis, BMD test was performed. In this study 40% had osteopenia or low bone mass and 7% had osteoporosis. About 93% of women above 80 years are either osteoporotic or having low bone mass.

Morbidity and Mortality
Both spine and hip fractures are associated with increased disability and mortality. Impact of fragility fracture is equivalent to stroke and myocardial infarction in geriatric population. Hip fractures have 34% excess mortality in first year in men. In female excess mortality is 20–24%. Death rate for hip fracture in elderly woman has now exceeded from stroke in certain European countries. Likelihood of death after 50 years of age in women is equal with breast cancer and hip fracture.

Most patients after hip fracture are not able to live independently. About 40% patients are not able to return to previous functional status.

Institutionalization/death rate is 39.2% within 2 years in female (>60 years) after hip fracture while it is 19.7% in control population. In male it is 52.1% while in normal population it is 12.4%.

Hospital bed occupancy days are much higher with hip fracture (568,000) in comparison to other chronic disease. In stroke it is 352,000 days while in chronic obstructive pulmonary disease it is 35,300 days.

Osteoporosis is not limited to female gender as 20% cases occur in male. In the United States, 2 million males are osteoporotic while many more are osteopenic.
Fragility fracture is the most drastic complication of low BMD that occur following minimal trauma.\textsuperscript{7}

Risk factors for fragility fracture:
- Low BMD (twofold increased risk for one SD decrease of BMD)
- Age (after 60 years with each decade risks increases by twofold)
- Previous fragility fracture (fivefold increased risk)

**Economic Effect**

In the USA, annual cost of fracture-related expenses secondary to osteoporosis was 13.8 billion in 1995 in comparison to asthma, which was 7.5 billion and congestive heart failure 20.3 billion.\textsuperscript{8} As baby boomers hit retirement age the cost by year 2050 will reach around 130 billion. In 2010, the cost of fragility fracture in the European Union was 37 billion and based on demographic changes it is predicted to double by 2050.

**Investigations**

BMD is measured by Dual-Energy X-Ray Absorptiometry (DXA). It is most commonly used test because of its accuracy and ease of using.\textsuperscript{9}

Bone densitometry report includes:
- **T Score**: Patient value is compared with young normal subject (peak bone mass) and expressed as number of SD above or below.
- **Z Score**: Patient value is compared with mean value of age matched normal subject and expressed as number of SD above or below.

Absolute BMD—It is the measured BMD (unit GM/CM\textsuperscript{2}).\textsuperscript{8}

**Limitation of DXA**

It measure bone density, that is, hydroxyl apatite per bone area. But it is altered by atherosclerosis (Aorta) and other degenerative changes due to calcification.\textsuperscript{10}

As two dimensional images in DXA, it does not identify minor details of the bone and its poor fracture prediction ability led to the development of new technique like TBS, HR PQCT.\textsuperscript{10}

BMD of spine and hip can predict fracture risk but there is a paradox, as most patients with fracture are osteopenic because of high population of this group.\textsuperscript{11}

**Indications of BMD Measurement**

- Age ≥65 (women) and ≥70 (men)
- Female with menopause and one risk factor
- Deformity, fracture, and osteopenia of vertebrae
- For analysis of response to therapy for osteoporosis
- Glucocorticoid therapy for more than 3 months
- Primary hyperparathyroidism
- Fracture in adults after age of 50\textsuperscript{12}

**Risk Factors for Osteoporosis**

**Non-modifiable**

- Age
- Race (Asian, Caucasian)
- Gender (female)
- Menopause (early)
- Built (slender)
- Family history\textsuperscript{5}

**Modifiable**

- Diet low in calcium and vitamin D
- Lack of estrogen
- Lifestyle (sedentary)
- Smoking
- Alcohol (more than two drinks/day)
- Caffeine (more than two serving/day)\textsuperscript{5}

About 70% of men with Osteoporosis have secondary cause. Among it alcohol abuse, glucocorticoid use, hypogonadism, and treatment with gonadotropin-releasing hormone (GnRH) analog are common causes.\textsuperscript{13}

**Diagnosis of Osteoporosis**

- **T Score** ≥1 (Normal)
- **T Score** between -1 and -2.5 (Osteopenia)
- **T Score** ≤-2.5 (Osteoporosis)\textsuperscript{8}

**Common Associated Conditions with Osteoporosis/Osteopenia**

**Diseases**

- **Endocrine disorder**: Thyroid disorder (hypo- and hyperthyroidism), hyperparathyroidism, hyperprolactinemia
- **Deficiency disorder**: Osteomalacia\textsuperscript{14}
GI disorder: Inflammatory bowel disease
Connective tissue disorder: Rheumatoid arthritis
Renal failure

Drugs
- Steroids
- Excess thyroid hormone
- Anti-epileptics
- Proton pump inhibitors

Treatment and Prevention

Non-pharmacological measures:
- Regular resistance and aerobic exercises
- Adequate calcium—1,000–1,200 mg/day for premenopausal women, men. For postmenopausal women and men 65 years or older it is 1,200–1,500 mg/day
- Adequate vitamin D (800–1,200 U/day)
- Limitation of alcohol and caffeine consumption, smoking cessations
- Fall prevention in elderly (risk for frequent falls are sedative, cognitive and visual impairment, disability, and obstacle to ambulation)

Pharmacological Therapy for Osteoporosis

Indications:
- Anyone with vertebral or hip fracture (fragility fracture) BMD not required
- T Score <2.5
- For osteopenia follow FRAX tool. Treatment is recommended for those having 10-year risk of 3% or more for hip fracture or 20% or more for other osteoporotic fracture

Types of medications:
- Antiresorptive agents:
  - Bisphosphonates
  - Raloxifene
  - Calcitonin
  - Estrogen
  - Denosumab (monoclonal antibody against RANKL)
- Anabolic agents:
  - Teriparatide (34 amino acid fragment of intact PTH)
  - Abaloparatide
  - Romosozumab

There is 30–70% reduction of vertebral fracture by these drugs. Osteoanabolic drugs reduces incidence of nonvertebral fracture 40–50% while antiresorbive drugs reduce it by 20–25%.

To determine efficacy of treatment BMD is repeated after 2 years. To determine serial changes, least significant change for particular instrument must be known.

There is a definitive treatment gap. As 40–95% of high-risk fracture patients do not receive treatment. In spite of benefit of treatment there is 50% reduction in the use of bisphosphonate in the USA. It is documented from 2008 to 2012 (crisis in osteoporosis).

Prevention of Fragility Fracture

- Prevention of first fracture is the most important step. There is five times high incidence of another fragility fracture after first fracture. Fracture liaison services (FLS) have been started in many countries to close the care gap. It is further evolved to identify the high risk groups to prevent the first fracture. In it dedicated coordinators work with endocrinologist and rheumatologist. They take care of all the aspects (identification, investigation, and intervention) of the disease.
- Frequent fall can be prevented by discontinuation of sedatives, correcting visual impairment, prescribing ambulatory aids, and hip protectors.

Conclusion

- Targeting young population for primary prevention will ultimately lead to decrease in health-care cost, disability, and death in geriatric population. So ultimate aim will be adequate bone mass in youth and policy for this is urgently needed.
- Most of the patients are not well informed about osteoporosis and its long-term impact and most patients believe that there is low to no increase in fragility fracture after first, despite contrary evidences.
- Like other chronic medical problems, osteoporosis also needs successful strategies for identification and treatment. As the population ages, number of patients will increase and there will be acute need for screening and prevention.
- Weak bone in elderly is a significant concern because it is associated with low quality of life and disability. Like in stroke, cancer, and myocardial infarction, fragility fracture is also linked with increased deaths, hospital admission, and impairment of health in elderly.
References

CHAPTER 84

Intermittent Fasting in Obesity—Hope or Hype?

Soumitra Ghosh

Abstract

Intermittent fasting is a form of calorie restriction that allows calorie intake on few days of the week (e.g., 2:5) or specific hours of the day (e.g., 8:16 or 10:14) and restricting the calorie intake at other times. It may be divided into alternate day fasting (ADF), modified ADF (MADF), and time restricted eating (TRE). In TRE food intake is limited to 8–10 hours in a day or lesser in sync with the external light-dark cycle and internal circadian clock. It has been seen that night shift workers are at increased risk of obesity, other metabolic diseases, and cancers. Short-term studies in humans have shown that TRE results in modest weight loss, fat loss, with improvements in insulin sensitivity, inflammatory markers, and triglyceride level. Intermittent fasting may offer greater improvements in body composition, metabolic, and inflammatory markers. Intermittent fasting may be advised to motivated individuals as one of the options of Calorie Restriction, keeping in mind that we have insufficient evidence on its beneficial effects on long-term obesity and chronic metabolic outcomes. Though it has been hyped by the press and the lay public, the scientific community has the hope and the wisdom to accept its promises as well as its limitations.

Introduction

Obesity is the result of an interplay of genetic, epigenetic, and environmental factors that impair the neurohormonal signaling that controls the satiety and hunger, and the calorie storage and expenditure. Despite the burgeoning problem, the treatment options of obesity are limited. Pharmacotherapeutic agents are limited by their insufficient targeting of obesity pathogenesis and significant adverse effects. Metabolic surgery, though currently the most effective means to treat obesity and its complications, has its share of short-term and long-term complications. Lifestyle modification in the form of appropriate diet, physical activity, and behavioral change forms the cornerstone of therapy.

Daily Energy Restriction: Challenges

An important component of lifestyle modification is restriction of energy intake to promote weight loss. Daily energy restriction (DER) where daily calorie intake is restricted is often not sustainable in the long run due to increased hunger, reduced energy expenditure, defense of body weight and other unknown factors. Research and advancements in intermittent energy restriction (IER) also known as intermittent fasting (IF) has raised from the quest for an alternative, more effective, and sustainable forms of energy restriction.

Intermittent Fasting/Intermittent Energy Restriction

Intermittent fasting is a form of calorie restriction (CR) that allows calorie intake on few days of the week or specific hours of the day and restricting the calorie intake at other times. There is no consensus on the exact definition of IF and different studies used different definitions. Broadly it may be divided into alternate day fasting (ADF), modified ADF (MADF), and time restricted eating (TRE). In ADF,
Intermittent Fasting in Obesity—Hope or Hype?

CHAPTER 84

497

patient fasts on alternate days. In MADE, patients fast on few days in a week, for example, 5:2. In TRE food intake is restricted to few hours of the day, 8–10 hours or less, for example, 8:16 or 10:14. There is no consensus on the amount of energy intake on fasting days, with energy intake ranging from 0% to 50% of non-fasting days in different studies.

**Potential Mechanisms of Benefit of Intermittent Fasting**

One basic idea of IF is that individuals do not fully compensate on non-fasting days for the reduced/absent calorie intake on fasting days thereby decreasing total calorie consumption. Proponents of intermittent fasting claim that it improves body composition and other obesity comorbidities.

“Fasting physiology” are adaptations developed by organisms during evolution to promote good health and to prolong survival by allowing repair and regeneration. In one very basic life-form yeast, addition of nutrients like glucose and amino acids blocks survival response and removal of these improves survival, while addition of water protects against DNA oxidative damage and use of alternative fuels by yeast as sources of energy.

In studies in both animals and humans, fasting has been found to reduce oxidative stress and promote autophagy. Autophagy is an evolutionary programmed cell repair process that recycles damaged organelles and misfolded proteins so as to prolong the lifespan of the cell. Autophagy is impaired in obesity, diabetes mellitus, and ageing. Fasting was also found to reprogram age-related pathways and hormones like Sirtuin 1, mTOR pathway, and IGF-1.

Another form of intermittent fasting (IF or IER) is TRE. In TRE food intake is limited to 8–10 hours in a day or lesser. Every organism has an internal circadian clock that is programmed to work in sync with the external light-dark cycle. The circadian system consists of a master clock in the suprachiasmatic nucleus of the hypothalamus and peripheral clock situated in other brain areas and the periphery. The entrainment factor (zeitgeber) for the master clock is light. The cellular oscillator is composed of a positive limb (CLOCK and BMAL-1) and a negative limb (CRYs and PERs). CLOCK and BMAL-1 dimerize in the cytoplasm and translocate to the nucleus. Transcriptional activators CLOCK and BMAL-1 promote the transcription of target genes period (PER) and cryptochrome (CRY) among others. The product of the target genes then forms a repressor complex which inhibits transcription of CLOCK and BMAL-1. Through this transcriptional-translational feed-back loop the master clock modulates rhythmic physiology of metabolism and other body rhythms. In normal circumstances cross-talk between the master and peripheral clocks synchronizes circadian rhythm with feeding behavior so that food intake occurs during the light period. From the metabolic perspective the circadian clock and circadian physiologic and biochemical rhythms partition metabolic processes according to the time of the day. Peripheral clocks are entrained by food too. Thus, when food intake occurs in the dark period, there is a desynchrony between the master and peripheral clocks, resulting in misalignment of metabolic processes resulting in obesity and its downstream complications.

The character of the gut microbiota is altered in obesity. A healthy gut microbiota is vast, complex, diverse, and have cyclical fluctuations in response to diet. The diurnal fluctuations in the gut microbiota in response to feeding and fasting modulate the activity of the gut microbiota, which in turn modulates metabolism. Therefore, fasting and eating in sync with the circadian rhythm would promote good metabolic health.

**Evidences in Animal Models**

TRF in rats in line with the circadian timing system (i.e., feeding during the active phase) improved glucose tolerance during the active phase, while TRF desynchronized with the circadian timing system (i.e., feeding during the inactive phase) worsened glucose tolerance. TRF increased bile acid synthesis, enhanced cholesterol excretion, and protected from inflammation.

A study in rats found that IF compared to daily CR protected the myocardium against ischemia-induced cellular damage and inflammation. IF was found to improve cognitive performance. CR and IF was found to improve longevity and resistance to age-related diseases in animal models.

In a study three groups of mice were subjected to either daily CR, ADF (with ad libitum food on every alternate day), or ad libitum food intake daily for a period of 20 weeks. It was seen that ADF mice compensated for periods of fasting by almost doubling the food intake on fed days. Therefore, the weight gain in ADF group was similar to
daily ad libitum feeding group. But the daily CR mice had significantly lesser weight. However, despite weight gain in the ADF, fasting glucose and insulin concentrations were similarly improved in ADF and daily CR groups, but such benefit was not seen in the daily ad libitum fed group. The findings suggest that the “fasting physiology” could have played a favorable effect on the improved metabolic profile and CR on fed days is equally essential for weight loss in ADF.

**Evidences in Humans**

Night shift workers are at higher risk for obesity, other metabolic diseases, and cancers. The increased risk of obesity is independent of calorie intake. Circadian misalignment for 10 days was associated with increased postprandial glucose, serum insulin, and increased mean arterial pressure.

Short-term studies in humans lasting from 4 days to 16 weeks have shown that TRE results in modest weight loss and fat loss. Improvements in insulin sensitivity, inflammatory markers, and triglycerides were seen. In humans, restriction of food intake to lesser hours in TRE was associated with a reduction in total calorie intake by 20%. This resulted in weight loss of ~4% at 16 weeks and was sustained for up to a year. However, the timing of TRE is very important. It may be early TRE (eTRE), that is, eating in the morning or delayed TRE (dTRE), that is, eating in the evening. In two weight loss intervention studies greater weight loss was seen in eTRE compared to dTRE, highlighting the importance of not only restricting the eating duration and prolonging the fasting duration; but also eating in sync with the circadian clock. In another 4-day randomized cross-over study, 11 overweight adults ate between 8 am and 2 pm (eTRE) and between 8 am and 8 pm (control schedule). Compared to control schedule, eTRE significantly decreased mean 24-hour glucose levels as well as glycemic variability. In eTRE group, a rise in ketones, cholesterol, expression of the stress response, anti-aging gene SIRT1 and the autophagy gene LC3A were seen before breakfast. It was thus concluded that eTRE improved 24-hour glucose levels, favorable lipid metabolism, circadian clock gene expression and autophagy, and may have anti-aging effects in humans.

Overweight subjects who consumed a low calorie (500 Kcal) but relatively high protein diet for 2 days in a week for 6 months (MADF) had lower abdominal fat, blood pressure, and improved insulin sensitivity. However, a review by Barnosky et al. found that daily CR was better than IF for weight loss, though both regimens improved insulin sensitivity and decreased visceral fat. A recent meta-analysis found that both IER and CER produced equivalent weight loss.

Another RCT comparing ADF, daily CR, and no-intervention found weight loss was similar between ADF and CR at 6 or 12 months. However, there was greater dropout in the ADF group. DEXA and MRI at week 24 found no difference between fat mass, lean mass, visceral, and adipose tissue mass between ADF and CR groups. In another small study of 11 patients, ADF participants had higher muscle expression of the SIRT1 gene. SIRT1 is known to be associated with longevity in humans. Unlike rodent studies most evidences suggest that calorie intake in ADF is not markedly increased on eating days in humans.

**Limitations of Current Evidences**

Most of the studies in animal and humans were small in size and of short duration. Therefore, effect of IER on long-term weight maintenance is unknown. There was no unanimity on the definition of IF across studies. Most studies did not study the effect of IF (IER) on other important parameters like appetite, mood, behavior, sleep, and physical activity. However, one reassuring fact of ADF in humans is that humans tended to not compensate (overeat on fed days) for the reduced calorie on fast days unlike rodents exposed to ADF with ad libitum food intake on fed days. Most evidences in humans suggest equivalent weight loss in DER and IER; proposing that CR is responsible for the weight loss. However, few studies reported improvements in metabolic and inflammatory parameters in IER highlighting the importance of “fasting physiology” and “circadian synchrony” that improves health and survival outcomes in humans. However, the optimal eating window in TRE is not clearly defined.

There are concerns about the applicability and the durability of IF in real world settings, where family and social factors, appetite, mood, and behavior pose challenges. Larger and longer studies in real world settings are needed to answer these questions. This will help answer the questions raised and also identify the individuals who would benefit from such a fasting regimen. There is an urgent need to have standardized definitions for the different forms of IER (IF); uniform methods...
for monitoring food intake; and optimal timing of food intake in TRE. The fasting regimens are not applicable in patients of diabetes mellitus on hypoglycemic agents. The long-term effect of IF on chronic diseases like diabetes, cardiovascular disease, cancers, and other degenerative disease is currently unclear.

Conclusion

Currently available evidence is insufficient for health-care professionals to recommend IF as standard practice. It is apparent that IF may benefit those who are motivated to lose weight. Any other energy restriction regimen would benefit only the motivated individuals and thus IF is no exception. Evidences in humans suggest that IF may offer greater improvements in body composition, metabolic and inflammatory markers despite similar weight benefits compared to DER. Therefore, currently IF may be advised to motivated individuals as one of the options for CR, bearing in mind that the benefits on weight loss may be similar to DER with possibly better improvement in other metabolic parameters with IF, and also accepting that we have insufficient evidence on its long-term applicability in real world settings or its beneficial effects on long-term chronic obesity outcomes. We may thus conclude that IF is another form of CR. Though it has been hyped by the press and the lay public, the scientific community has the hope and the wisdom to accept its promises and limitations.

References
