Cutting the fat out

THE FOCUS HAS COME BACK TO FINDING NON-INVASIVE WAYS TO REDUCE BODY WEIGHT, SAYS **S ANANTHANARAYANAN**

With diets and exercise proving only mildly effective in weight reduction, there is more and more reliance being placed on surgical methods to reduce food intake and metabolism to save the obese from a host of troubles that arise from overweight. But surgery, although undoubtedly effective, is often not "palatable" and also has its own problems. A discovery that surgery depends on other factors to have results has renewed the quest for methods to control weight gain without the need for this procedure.

Karen K Ryan, Valentina Tremaroli, Christoffer Clemmensen, Petia Kovatcheva-Datchary, Andriy Myronovych, Rebekah Karns, Hilary E Wilson-Perez, Darleen A Sandoval, Rohit Kohli, Fredrik Backhed and Randy J Seeley, of Ohio, Cincinnati, Gothenburg in Sweden and Copenhagen report in the journal *Nature* their finding that surgery, which seems to mechanically impede over-eating or the assimilation of food, still does not prove effective if a genetic feature is not present.

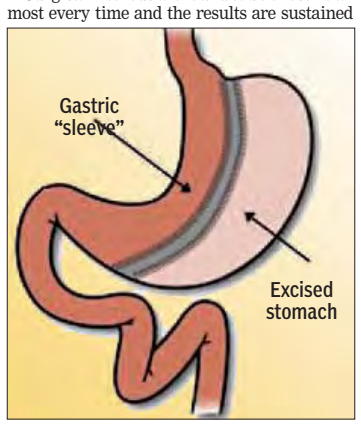
Obesity is classified as a disease and is considered the one main preventable cause of death in current times. Overweight is directly implicated in heart disease, Type 2 diabetes, a disease of breathing obstruction during sleep, some kinds of cancer, degeneration of the bones and asthma. Records show that the overload of body weight is a major cause for the need of knee and hip replacements. And there are conditions where reduction of body weight is an imperative for survival.

While active living style and moderation in consumption of food are certainly the best ways to weight control, the reason for overweight may be genetic, medical or psychiatric. The increased availability and use of attractive, high-calorie "fast food", use of private and public transport and mechanisation of much that was done manually are causes that have increased in modern times. Other reasons for the increase in obesity are identified or suspected as lack of sleep, hormonal imbalance due to pollution or contaminants or some medicines, stable ambient temperature, thanks to airconditioning, and the rise of genetically overweight populations because of economic or social reasons. But the bottomline is that obesity, or unreasonable weight gain, is a disease with serious implications and there are situations where it is vital that it be reversed.

Bariatric surgery

Where there are reasons that a person is not able to reduce food intake or increase exercise, or the overweight is due to other reasons, the solution that is available and sometimes unavoidable is surgery. By surgery we mean not the "liposuction", which is cosmetic, but of the stomach and digestive system, to restrict the amount of food that can be taken or to interfere with assimilation. Methods include reducing the size of the stomach with a band, or removing a part of the stomach or bypass of a portion of the small intestine. A common procedure used is *Vertical Sleeve Gastrectomy*, where 80 per cent of the stomach is removed by surgically reshaping the bulge shape into a sleeve that matches the food pipe and the beginning of the small intestine. The procedure is carried out laproscopically and is becoming widespread and carried out even on children and adolescents. This practice has been found to be so successful in weight control that it has replaced other methods, like bypass of a part of the intestine. The method has been found to be clearly effective and also superior to other medical methods of managing overweight or diseases that arise for obesity.

Surgical methods are found to be effective almost every time and the results are sustained and long-term. There is a marked improvement in all associated medical conditions and diabetes is found to be fully controlled within a year in 40 per cent of the cases.



While VSG has thus become the way to go for the overweight, there are negatives that do not make surgery an easy choice for all patients. For one, the procedure is non-reversible. The reduction in food intakes is because the patient feels nausea as soon as the restricted stomach is full and he/she stops eating to avoid discomfort, rather than out of satiation. And then, there are the risks of surgery and complications, such as "sleeve leaks", clots and infection, damage to the *Vagus* nerve, which causes constant nausea, vomiting and disturbance in the normal passage of food. There is, hence, the need for alternative, non-surgical methods. But the great effectiveness and wide use of VSG has led to a feeling that it is the only "way to go".

On the face of it, it would appear that the results of VSG come from reduction in food intake because of a physically smaller stomach — a form of mechanical intervention. And the simplicity of this explanation suggests that there is nothing more to be said — the root of the trouble is in filling the stomach and if the stomach is made smaller, it settles the matter. But there is evidence that only reduction of size may not be the mechanism leading to disease remission. For one, it is found that most diabetic patients are able to go off diabetes medication within days of surgery. But in this short time there is hardly any substantial weight reduction.

How, then, to explain the dramatic relief? There is, hence, doubt about mechanical reduction being the reason for VSG results and it would appear that VSG affects other processes. It has been suggested that the results arise from changes in gut physiology, changes in nerve-mediated signalling or the nature of microbes that populate the intestines.

A well-known result of weight reduction surgery is that there are changes in the circulation of bile acids, the secretions of the liver, which are used in the assimilation of fats. It has also been established that in addition to the mechanical digestion and absorption of fats, bile acids combine with a factor known as *FXR*, which plays a role in the metabolism of fats. In the light of this effect of VSG, the group of researchers examined the role that the FXR link may have in regulating metabolism and the microbial environment of the gut.

Testing the link

To test out this possibility, the researchers carried out VSG surgery on groups of mice that were obese by being overfed. One group of mice had been genetically modified to lack the FXR factor and the other group was of unmodified mice from the same litter. They used methods of analysis of the behaviour of cells to trace the biological processes that got changed after VSG. The group had earlier established that VSG had a major effect on the way genes of the liver acted in regulating fats.

They now found that the biological pathway that led to metabolism and conversion of fats was the key beneficiary of VSG. Of other pathways strongly benefitted, several were found to point to changes in microbe populations.

The trials clearly established that it was only the mice that had the FXR process intact that benefited from VSG. There was weight loss and appetite restriction of the modified group too, but this was not sustained and this group soon lost the apparent benefit. Even in respect of the changes in the microbe populations in the gut, which affected weight gain and glucose control, it was found that VSG had a significantly greater effect on mice that had the FXR factor than the ones that did not.

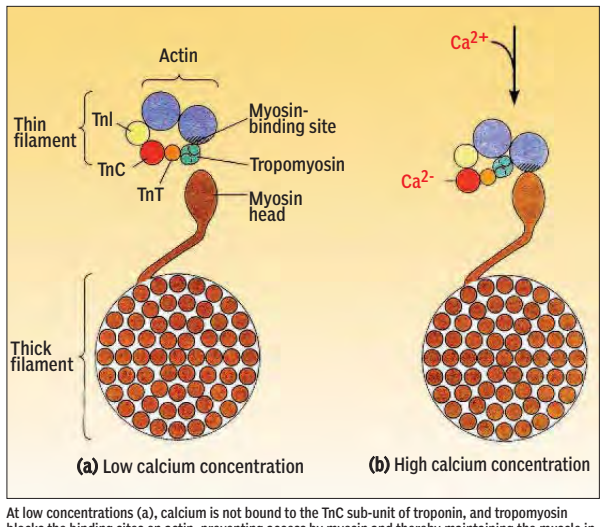
These are significant findings as they point to mechanisms of weight control through VSG that are quite different from pure dimensional reduction of the stomach volume. As an FXR-linked mechanism is demonstrated, it suggests that there could be other means of reaching the desired end without the need for surgery.

THE WRITER CAN BE CONTACTED AT simplescience@gmail.com

RECOGNISING THE SITES

THE REGULATION OF MUSCLE CONTRACTION DEPENDS ON CALCIUM, WRITES **TAPAN KUMAR MAITRA**

Muscle contraction implies that skeletal muscle ought to contract continuously, as long as there is sufficient Adenosine triphosphate (ATP). Yet experience has it that most skeletal muscles spend more time in the relaxed state than in contraction. Contraction and relaxation must, therefore, be regulated to result in the coordinated movements associated with muscle activity.



At low concentrations (a), calcium is not bound to the TnC sub-unit of troponin, and tropomyosin blocks the binding sites on actin, preventing access by myosin and thereby maintaining the muscle in the relaxed state; at high concentrations (b), calcium binds to the TnC sub-unit of troponin, inducing a conformational change that is transmitted to tropomyosin.

The regulation of muscle contraction depends on free calcium ions (Ca^{2+}) and on the ability of the muscle cell to raise and lower calcium levels rapidly in the cytosol (the sarcoplasm in muscle cells) around the myofibrils. The regulatory proteins tropomyosin and troponin act in concert to regulate the availability of myosin-binding sites on actin filaments in a way that depends critically on the level of calcium in the sarcoplasm.

To understand how this process works, we must begin by recognising that the myosin-binding sites on actin are normally blocked by tropomyosin. For myosin to bind to actin and initiate the cross-bridge cycle, the tropomyosin molecule must be moved out of the way. The calcium dependence of muscle contraction is due to troponin C (TnC), which binds calcium ions. When a calcium ion binds to TnC, it undergoes a conformational change that is transmitted to the tropomyosin molecule, causing it to move toward the centre of the helical groove of the thin filament, out of the blocking position. The binding sites on actin are then accessible to the myosin heads, allowing contraction to proceed.

When the calcium concentration in the sarcoplasm is low ($<10^{-4}$ m*M*), tropomyosin blocks the binding sites on the actin filament, effectively preventing their interaction with myosin. As a result, cross-bridge formation is inhibited and the muscle becomes or remains relaxed. At higher calcium concentrations ($>1(T^{3}$ mM), calcium binds to TnC, causing tropomyosin molecules to shift their position, which allows myosin heads to make contact with the binding sites on the actin filament and thereby initiate contraction.

When the calcium concentration falls again as it is pumped out of the cytosol, the troponin-calcium complex dissociates and the tropomyosin moves back to the blocking position. Myosin binding is, therefore, inhibited, further cross-bridge formation is prevented and the contraction cycle ends. Thus, an increase in the sarcoplasmic calcium concentration stimulates the contraction of skeletal muscle by triggering the following series of events:

- Calcium binds to troponin and induces a conformational change in the complex.
- This change in troponin causes a shift in the position of the tropomyosin with which it is complexed.
- The binding sites on actin become available for interaction with myosin.
- Cross-bridges form, setting in motion the sequence of events that leads to contraction.

Muscle contraction is regulated by the concentration of calcium ions in the sarcoplasm. But how is the level of calcium controlled? Think for a moment about what must happen when we move any part of our bodies — when we flex an index finger, for instance. A nerve impulse is generated in the brain and transmitted down the spinal column to the nerve cells, or motor neurons, that control a small muscle in the forearm. The motor neurons activate the appropriate muscle cells, which contract and relax, all within about 100 millisecond. When nerve impulses to the muscle cell cease, calcium levels decline quickly and the muscle relaxes.

Therefore, to understand how muscle contraction is regulated, we need to know how nerve impulses cause calcium levels in the sarcoplasm to change and how these changes affect the contractile machinery.

Muscle cells have many specialised features that facilitate a rapid change in the sarcoplasmic concentration of calcium ions and a rapid response of the contractile machinery.

THE WRITER IS ASSOCIATE PROFESSOR, HEAD, DEPARTMENT OF BOTANY, ANANDA MOHAN COLLEGE, KOLKATA, AND ALSO FELLOW, BOTANICAL SOCIETY OF BENGAL, AND CAN BE CONTACTED AT tapanmaitra59@yahoo.co.in

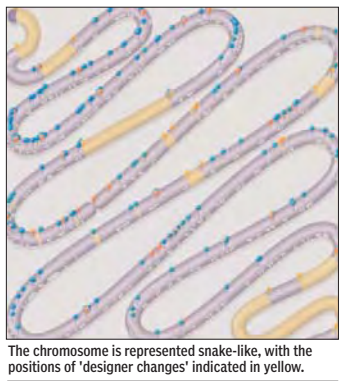
Towards synthetic life

THE ACHIEVEMENT, AS **STEVE CONNOR** FINDS OUT, IS AKIN TO 'CLIMBING MOUNT EVEREST' IN ITS COMPLEXITY

Scientists have made the first artificial chromosome that is both complete and functional in a milestone development in synthetic biology, which promises to revolutionise medical and industrial biotechnology in the coming century. The researchers built the artificial chromosome from scratch by stitching synthetic strands of DNA together in a sequence based on the known genome of brewer's yeast. They predict that a completely synthetic yeast genome comprised of its entire complement of 16 chromosomes could be made within four years.

"Our research moves the needle in synthetic biology from theory to reality. This work represents the biggest step yet in an international effort to construct the full genome of synthetic yeast," said Jef Boeke of the New York University School of Medicine, a lead author of the study published in the journal *Science*. "It is the most extensively altered chromosome ever built. But the milestone that really counts is integrating it into a living yeast cell. We have shown that yeast cells carrying this synthetic chromosome are remarkably normal. They behave almost identically to wild yeast cells, only they now possess new capabilities and can do things that wild yeast cannot (do)," he said.

"Not only can we make designer changes on a computer, but we can make hundreds of changes through a chromosome and we can put that chromosome into yeast and have a yeast that looks, smells and behaves like a regular yeast, but this yeast is endowed with special properties that normal yeasts don't have," he explained.



The chromosome is represented snake-like, with the positions of 'designer changes' indicated in yellow.

The synthetic yeast chromosome was based on chromosome No. 3, but scientists deleted large parts of it that were considered redundant and introduced further subtle changes to its sequence — yet the chromosome still functioned normally and replicated itself in living yeast cells, they said. "We took tiny snippets of synthetic DNA and fused them together in a complex series of steps to build an essentially computer-designed chromosome 3, one of the 16 chromosomes of yeast. We call it 'synIII' because it's a completely synthetic derivative that has been engineered in a variety of interesting ways to make it different from the normal chromosome," said Boeke.

The achievement was compared to climbing Mount Everest in its labour-intensive complexity, as it involved stitching together 273,871 individual building blocks of DNA — the nucleotide bases of the yeast's genes — in the right order, and removing about 50,000 repeating sequences of the chromosome that were considered redundant.

"When you change the genome, you're gambling. One wrong change can kill the cell. We have made over 50,000 changes to the DNA code in the chromosome and our yeast still lived. That is remarkable, it shows that our synthetic chromosome is hardy, and it endows the yeast with new properties," said Boeke.

Britain is one of several countries involved in the international effort to synthesise all 16 yeast chromosomes. Last year, the government announced that it would spend £1 million on the yeast project out of a total budget of £60 million it has dedicated to synthetic biology.

Paul Freemont of Imperial College London said that the first complete and functional synthetic yeast chromosome was "a big deal" and significant step forward from the work by DNA scientist Craig Venter, who synthesised the much simpler genome of a bacterium in 2010. "It opens up a whole new way of thinking about chromosome and genome engineering as it provides a proof of concept that complicated chromosomes can be redesigned, synthesised and made to work in a living cell," he said.

Artificial chromosomes designed by computer will be vital for the synthetic life-forms that scientists hope to design for a range of applications, such as the breakdown of persistent pollutants in the environment or the industrial manufacture of new kinds of drugs and vaccines for human and animal medicine.

"It could have a lot of practical applications because yeast is used in the biotechnology industry to produce everything from alcohol, which has been produced for centuries, to biofuels and speciality chemicals to nutrients. Yeast is a really interesting micro-organism to work on because it has an ancient industrial relationship with man. We've domesticated it since the days of the Fertile Crescent and we've had this fantastic collaboration to make wine, break and beer," said Boeke.

"That relationship persists today in a wide range of products that are made with yeast such as vaccines, fuels and specialty chemicals and it's only going to be growing. Yeast is one of the few microbes that packages its genetic material in a nucleus just like human cells. So it serves as a better model for how human cells work in health and disease," he added.

THE INDEPENDENT

PLUS POINTS

Through the Borealis

A small National Aeronautics and Space Administration-funded rocket launched in Alaska earlier last month glided through the emerald "auroral curls" of the Northern Lights and formed part of the space agency's Ground-to-Rocket Electrodynamics-Electrons Correlative Experiment, which will study the transfer of energy from the sun to earth — in this case, the Aurora.

"Auroral curls are visible from the ground with high-resolution imaging," said Marilia Samara, a lead investigator and a space scientist at Texas' Southwest Research Institute. "And we can infer from those observations what's happening farther out. But to truly understand the physics we need to take measurements in the aurora itself."

The rocket launches straight into an aurora over Venetie, Alaska.

The rocket took measurements of particles and electric fields during its 10-minute flight, with scientists hoping to better understand how the curls form out of the plasma (superheated gas) inside the Aurora Borealis, and learn more about how the sun interacts with earth's magnetosphere. "The conditions were optimal," Samara added. "We can't wait to dig into the data."

CHRISTOPHER HOOTON/THE INDEPENDENT

Earl Grey benefit

There's another reason to put the kettle on and make a brew – drinking tea could help tackle heart disease, according to a study. Bergamot extract, the key ingredient in Earl Grey tea, was found to lower cholesterol. Researchers said the fragrant Mediterranean fruit that gives Earl Grey its unique flavour contains enzymes known as Hydroxy Methyl Glutaryl Flavonones, which can attack proteins in the body known to contribute to cardiovascular disease. And bergamot could even be as effective as statins, the group of medicines used to lower the level of cholesterol in the blood.

The study, carried out by scientists at Italy's University of Calabria, used concentrations of HMGF on the proteins that cause heart disease.

Writing in the *Journal of Functional Foods*, they said a dietary supplement of HMGF could be just as effective as statins in combating Low-Density Proteins or "bad" cholesterol. Additionally, HMGF was also found to increase levels of High-Density Lipoproteins or "good" cholesterol.

The journal's report said, "High cholesterol is a common health concern for us all and often statins are given to help treat the condition.

Extract from bergamot – most commonly used in Earl Grey tea – reduced total cholesterol and LDL levels but there was an increase in HDL levels. Therefore, a daily supplement of bergamot fruit extract could be very effective for the treatment of high cholesterol."

The citrus fruit has long been known as a "superfood" that can protect against cardiovascular disease. In 2012, research led by the University Magna Graecia in southern Italy and published in the *International Journal of Cardiology* reported similar findings about the cholesterol-reducing effects of bergamot. Extracts from the fruit have also traditionally been used to treat wounds, inflammation and as an antiseptic.

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Drone zones

Drones — or at least talk of them — were everywhere in 2013. The unmanned aerial vehicles that have already changed how the USA wages war have the potential to revolutionise law enforcement, wildlife monitoring, news gathering and, as Amazon CEO Jeff Bezos said, package delivery. Drone plans are taking shape across numerous industries as USA awaits new guidelines from the Federal Aviation Administration, due in 2015, on the domestic use of unmanned aerial vehicles. In the absence of regulatory language, entrepreneurs and technophiles such as Bezos have dreamed up ambitious plans for drone use, just as others have sounded the alarm about the potential for drones to malfunction catastrophically or even fall prey to hackers.