

# Matters of the Heart

A publication by Academy of Cardiovascular Sciences  
(International Academy of Cardiovascular Sciences – India Section)

**Volume 3; No.1**

**January 2019**

There is an urgency to extend initiatives for cardiovascular health protection, such as increasing awareness for improved life style, nutritious and healthy food, and promote health wellness programmes to combat heart diseases. "*Matters of the Heart*" is designed to provide public health education in these areas.

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## **CONTENTS**

### **High Blood Pressure in Childhood – a Matter of Concern**

*Sanjay Ganesh MD, DM*

### **Childhood Obesity**

*S. Jayaram Das MD, DM, FRCP, FRCPI,FRCP-CH*

### **3D Bioprinting of Heart and Blood Vessels: A Near Reality**

*Mira Mohanty MD, FICPath*

### **Gestational Diabetes: Spoiler of the Motherhood Moment**

*Surya Ramachandran PhD*

### **‘Blowing off Steam’ by Vigorous Exercise Increases Heart Attack Risk**

*Sumi S PhD*

### **Mysterious DNA Regions and Heart Disease Risk**

*Vikas Kumar MPharm*

### **The Beginning of A New History**

*Jayalekshmi VS MSc*

### **Heart Health with Soya Beans**

*Ciji Varghese MSc*

## HIGH BLOOD PRESSURE IN CHILDHOOD – A MATTER OF CONCERN



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Cerebrovascular accident, also known as stroke, 'strikes' nearly one in twenty people by the age of 65 years. More than half of this is attributed to high blood pressure (hypertension), which is the strongest risk factor for developing a stroke. Apart from stroke, hypertension is also responsible for a sizeable proportion of heart attacks, heart failure and kidney diseases in the community. One-fourth of the population is expected to be hypertensive by 2025 in India. Hypertension is responsible for more than 10 percent of all deaths in adults. Apart from the poignant picture it embosses on the health status of individuals, communities and humanity as a whole, the economic impact of

this disease is immense. An analysis conducted a few years ago revealed that the annual loss of income attributable to hypertension alone amounted to 43 billion rupees in India<sup>1</sup>. Till recently, hypertension was considered to be a disease affecting adults. However, data is emerging from all parts of the globe to substantiate those children and adolescents are also affected, rendering them at a disadvantageous health position during adulthood.

### **What is childhood hypertension?**

The diagnosis of hypertension in childhood depends on the measured blood pressure as well as a few other parameters. Unlike adults, who have uniform blood pressure “cut offs” for categorization into normal and abnormal values, the criteria for defining hypertension vary from child to child. After recording the blood pressure, the health-care personnel will refer to a chart to identify the cut-off limits based on sex, age and height; and verify if the child has hypertension, elevated blood pressure not amounting to hypertension (*previously termed as pre-hypertension; this can be considered as marginally elevated blood pressure*) or normal blood pressure. This chart or table contains the cut-off values for boys and girls categorized by age and height. The revised diagnostic criteria formulated by the American Academy of Paediatrics in 2017 for hypertension in childhood, has been listed in table 1.<sup>2</sup>

**Table 1. Definitions of blood pressure categories and stages of hypertension in children**

<b>CATEGORY</b>	<b>For Children aged 1-13 years</b>	<b>For children aged &gt;13 years</b>
<b>Normal BP</b>	BP < 90 <sup>th</sup> percentile for sex, age, height	BP < 120 / <80 mm Hg
<b>Elevated BP:</b>	≥90 <sup>th</sup> percentile to <95 <sup>th</sup> percentile or 120/80 mm Hg to <95 <sup>th</sup> percentile (whichever is lower)	120/<80 to 129/<80 mm Hg
<b>Stage 1 Hypertension</b>	≥95 <sup>th</sup> percentile to < (95 <sup>th</sup> percentile + 12 mmHg), or 130/80 to 139/89 mm Hg (whichever is lower)	130/80 to 139/89 mm Hg
<b>Stage 2 Hypertension</b>	≥ (95 <sup>th</sup> percentile+12mm Hg), or ≥140/90 mm Hg (whichever is lower)	≥140/90 mm Hg

Though the criteria may appear complicated for a quick reading, it is remarkable in that for older children (aged 13 and above), the definitions have been simplified and appear in line with the criteria used for adults.

### **Burden of the problem**

As in adults, childhood hypertension often occurs without any underlying causative disease, which is termed primary

hypertension. Such children are usually overweight or obese, and their parents or siblings too are likely to be having similar health issues such as hypertension, obesity, diabetes or lipid abnormalities. Their blood pressure values are usually elevated only mildly, unlike in children in whom hypertension is secondary to another disease (e.g., diseases of kidney, certain endocrine and metabolic diseases).

The occurrence of primary childhood hypertension is considered to be on the rise globally. Previous estimates from community surveys in the United States amounted to 3.6 percent prevalence of hypertension in children aged 3 to 18 years. However, recent studies suggest that more than one-tenth of the children are hypertensive.<sup>3</sup> In India, school surveys provide an insight into the problem. A study of about 21000 school children aged 5 to 15 years in Kerala revealed alarming trends. One-tenth of the normal-weight children had high BP recordings, whereas 17% of the overweight children were found to have hypertension.<sup>4</sup> Estimates of childhood hypertension vary between 5 to 10 percent in similar school surveys conducted in India. Another matter of concern is the rising burden of obesity in this age group which could further worsen the scenario of childhood hypertension. The socio-cultural factors driving hypertension and obesity in childhood are commonplace in this era of urbanization. Physical inactivity due to lack of open spaces, insecure neighbourhood and academic pressures divert the children to readily accessible indoor leisure activity such as television

and electronic devices. Equally contributory are the easily available convenience or junk food rich in calories and salt.

### **Consequences of high blood pressure in childhood**

Elevated blood pressure can evolve into frank hypertension during childhood itself. In fact, about one in 15 of children who have elevated BP but not amounting to hypertension have been found to progress annually. Moreover, these children carry hypertension into adulthood, similar to a “conveyor-belt”. Studies in such children have proven that high blood pressure brings about structural changes such as thickening of heart and hardening of blood vessels early on in life. Hypertension co-exists with other high-risk factors described previously, like excess body weight, changes in metabolism predisposing to diabetes and lipid abnormalities. Hypertensive children also are likely to be less active physically, with impaired tolerance to exercise. The combination of all these risk factors result in higher risk of developing major ailments such as heart attack, stroke and kidney disease early on in life.

Morbidity and risk of the disease apart, such ailments often affect the emotional well-being of individuals and families. Parents, older children and young adults get anxious about the health consequences, the need to take medicines for an indefinite period, education and career prospects. Quite naturally, they also worry about any adverse effects of the medicines.

## Strategies for control and future perspectives

Primary hypertension can often be treated with changes in lifestyle and diet. Increasing intake of fruits and vegetables, improving the physical activity of the children, adoption of weight management go a long way in reversing primary hypertension in childhood. A few children with persistent hypertension need medications. However, secondary hypertension requires use of medicines to control BP along with treatment of the underlying disease.

The benefits of intervention for hypertension at community level and for an individual are huge. WHO has observed that hypertension is an easily preventable non-communicable disease. It is estimated that 2% reduction in diastolic blood pressure could potentially prevent 3,00,000 deaths from cardiovascular diseases in India. The benefits are reaped early when identification and rectification commence from young age itself. However, the biggest challenge in childhood hypertension lies in its detection itself. Unlike adults, BP measurements are seldom performed in clinics for children. Awareness about this entity and its consequences is quite low among the public.

Early detection might be facilitated by school health checks and surveys, which also help to educate the children about hypertension and allied health problems. Introducing the concept of childhood hypertension to any adult with cardiovascular disease or risk factors during their medical



visits could help to screen the children in their family, who are at higher risk to acquire such diseases and adopt preventive measures. Interventions using community health workers, school health talks, discussions in media are all useful strategies in this regard.

Actions at multiple levels starting from home are required to combat the menace of hypertension and other life-style diseases in childhood. Restricting the time spent on electronic gadgets and televisions, access to convenience food as well as eating-out from early childhood are useful. Kids should be trained in activities like swimming and cycling and encouraged to play outdoors in secure areas. School-and community-based interactions should aim at improving physical activity, checking convenience-food use and inculcating a healthy diet culture. Many schools have started discouraging children from bringing high calorie snacks and have banned “junk food and soft-drinks” in their canteens. Legislations regarding food-labelling with respect to calories and salt, regulations in selling packaged and high convenience food to children, setting up public areas, parks, cycling tracks and playgrounds are some of the actions required at the level of policy-makers. Healthcare services intervene by holding field surveys, maintaining a community database, organize health talks, camps, counselling the families at risk, implementing balanced nutrition to expectant mothers and monitoring growth of babies. It is said that providing excessive nutrition for low-birth weight and stunted babies can predispose to obesity.

In a nutshell, concerted efforts to disseminate information regarding hypertension, identification of children at risk, institution of preventive strategies and timely treatment and monitoring will curtail it from blooming into a major public health problem threatening the fitness and economy of the upcoming generation.

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## CHILDHOOD OBESITY



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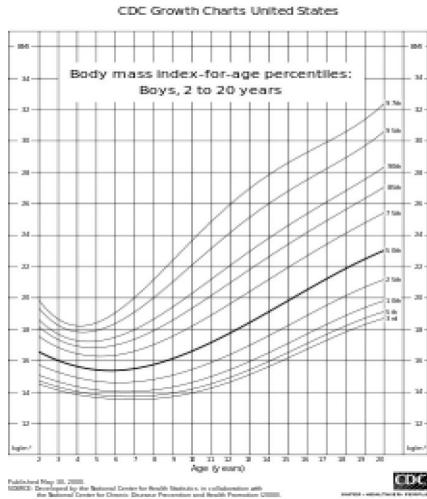
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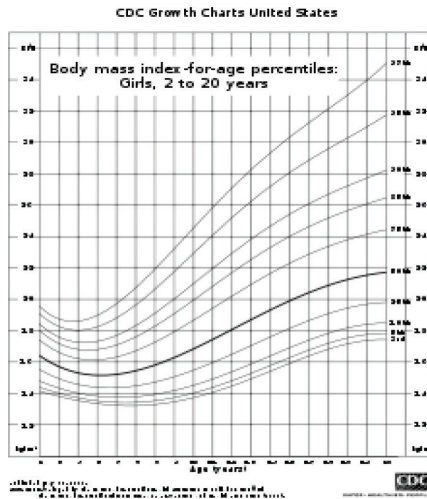
Obesity is probably the most important public health problem affecting human beings today, sparing only few very poor regions with chronic food scarcity, like sub-Saharan Africa. In 2010 overweight and obesity were estimated to cause 3.4 million deaths, 3.9% years of life lost and 3.8% of disability-adjusted life-years (DALYs) worldwide<sup>1</sup>. In USA 35.7% of adults are obese<sup>2</sup>. National Health & Nutrition survey there in 2009-10 found 17% of 2-19 years old to be obese. If you look at studies in the last 25 years, there are lots of discrepancies in the numbers. This is because of

the lack of agreement on the criteria for classification. Now, all the international bodies have agreed that BMI ( Body Mass Index) = weight in Kilograms / (height in meters)<sup>2</sup> would be the scale used to measure and classify as overweight or obesity<sup>3</sup>. For adults - >30 BMI is classified as obesity and 25-30 BMI is the overweight range. >2 years old children with a BMI > 95<sup>th</sup> percentile meet criteria for obesity and BMI between 85<sup>th</sup> and 95<sup>th</sup> percentile is the overweight range. Most obese children grow up to obese adolescents and eventually obese adults. Thus, childhood obesity is to a great extent the mother of adult obesity. Hence, if we are serious about tackling this problem we should start with childhood obesity and prevent them marching on to obesity in later life. In India the situation is still in a heterogeneous state. We still have rural areas with lack of availability of sufficient food & resultant under nutrition. Visibly, in urban areas obesity dominates - a dramatic change in the last 50 years. Obesity is efficiently replacing under nutrition as a worldwide health hazard and this is happening in India as well. There are some endocrine & genetic causes of obesity and these few are not for detailed discussion here, because our aim is to prevent and control this eminently preventable global disaster in those who would have otherwise been healthy.

**Below is BMI charts for Boys & Girls :**



*BMI for age percentiles Boys 2 to 20 yrs.*



*BMI for age percentiles Girls 2 to 20 yrs.*

## Causes

In the carnivorous animal kingdom, hunger dictates hunting and killing of the prey & feasting on it. Once satiety is achieved, there is no further killing. Humans have the capacity to store energy in adipose tissue, allowing improved survival in times of famine. Furthermore humans innately prefer sweet & salty foods & reject bitter flavors. These probably reflect evolutionary adaptations to avoid consuming toxic plants. Exposure to the sweet & salty foods promotes their acceptance & liking. Liking can lead to repeated consumption of such food, even when they are not required, and eventually to a level of being addicted to them. In simple terms Obesity is the result of an imbalance of caloric intake & energy expenditure. Individual adiposity is the net result of a complex interplay of genetically determined body habitus, appetite, nutritional intake, physical activity & energy expenditure. Certain factors that are known : pregnant ladies who are obese tend to have more large for dates babies & babies who are large at birth tend to grow up as obese children<sup>4</sup>. Environmental factors determine levels of available food, preferences for types of food, levels of physical activity & preferences for types of activities.

## Environmental changes

In the last 4 decades food environment has changed dramatically. From extended families to nuclear families now.

Eating used to be a family affair with timings. Hunger for food used to be recognized & satiety was also given respect as the stop signal. In the nuclear families, with both partners working, cooking at home has come down. Commercial foods are a lot more easily available - a phone call or a message and food is delivered home. Food prices have also come down, in relation to family budget. In addition marketing pressures have resulted in larger portion sizes.

**Snacking** - eating between meals, while seeing T.V., while watching/working on computer/mobile is a new habit. This has no relation whatsoever to hunger, thirst or satiety. Hunger does not come into play here and satiety as the stoppage signal is given no chance. The type of the food taken like this also matters. The bites are by and large finger foods which are high in fat and calorie content. There has been an increase in consumption of high carbohydrate beverages along with these. Almost always this is a sedentary habit - unwanted input with hardly any expenditure. Again, in simple terms calories are almost continually put in when there is no need for them and all that the body can do is to store them as fat in various places. Retrieval from these stores are hardly needed in the above type life style, where continual input goes on.

**Fast foods** - One-third of children in USA consume fast food daily. A typical fast food can contain 2000 K.cal & 84 gm. of fat. Many children take 4 servings of high carbohydrate beverages per day - additional 560 K.cal. of low nutritional value - from

high fructose corn syrup. Though we don't have actual figures, this type of eating habits are fast catching up in cities in India. It should not be much different in other parts of the developing countries.

***Physical activity*** - has come down dramatically. Walking to school is a memory of the past. Transport is always available. In the school curriculum, academic performance pressures have led to reduction in physical education. T.V., Computers & video games are all sedentary activities that do not burn calories. Extra time spent in the above activities leads to reduction in sleep & that is conducive to weight gain and obesity<sup>5</sup>.

## **Effects on Health**

### ***Psychological***

The first problems to occur in obese children are emotional or psychological. Bullying by peers & some are harassed by their own family. This may lead to low self esteem and depression.

### ***Physical***

Almost all the organs can be affected:

Endocrine - impaired glucose tolerance, diabetes mellitus, metabolic syndrome, hyperandrogenism, effects on growth & puberty, nulliparity & nulligravidity.



Cardiovascular - hypertension, hyperlipidemia and increased risk of coronary heart disease as an adult.

Respiratory-obstructive sleep apnea & obesity hypoventilation syndrome.

Gastrointestinal - Nonalcoholic fatty liver disease, cholelithiasis.

Musculoskeletal - slipped capital femoral epiphysis, tibia vara.

Neurological - idiopathic intracranial hypertension.

Psychosocial - distorted peer relationships, poor self esteem, anxiety, depression.

Skin - furunculosis, intertrigo.

### ***Long term effects***

They are more at risk for adult health problems such as heart disease, type 2 diabetes, stroke, osteoarthritis and several types of cancer - and all occurring earlier.

### **Recognition**

Recognition is the first and most important step. This involves the treating doctor identifying that the child is not healthy and then the family and the child appraised appropriately. Attempt must be made to check height & weight of all children at each health visit and plot them on to the BMI graph. Once

this is done, the actual nutritional status of the child would be evident and that gives us an opportunity to recognize the problem early enough, demonstrate the situation objectively to the parents and counsel them at a time when they are likely to be receptive. It is important to follow up these children and serially monitor their BMI. However, after the initial few years of hospital visits for immunization, there are no mandated health visits. This is the situation after the age of 5 years and into adolescence. When one looks at the prevalence and progression of obesity, it is exactly the above period that is crucial for recognition and early corrective action. We need to seriously invent a way to get them for health visits, when they and their family think they are doing well. This is a challenge.

### **Investigations**

Investigations have to be individually tailored. In general investigate for any medical diseases that could have led to the obesity. The second group of investigations are aimed at looking for the severity of known associations or complications of obesity. These would help in optimal management to correct and prevent future problems.

### **Treatment**

Therapy is by a team comprising of the primary treating pediatrician, the nutritionist and other sub-specialists as required. The plan of therapy depends on the child's age, whether the baby is overweight or obese and whether there

are any complications. There is no effective pharmacotherapy resulting in reversal of excess adiposity in children and adolescents. The few drugs available are licensed for use in adults. Therapies like bariatric surgery /procedures are licensed only after bone growth is completed.

In short, therapy is long and in principle involves gradual but steady reduction in the input of calories and concurrent increase in physical activities which would burn calories and hoping that these calories come from the excess fat stores. This is a real tedious process for the concerned child, their parents and family members and the involved treating team. Results are very slow to be visible and major barriers are the financial clout of the big fast food industry. Radio, TV & mobile are all used by the powerful advertising industry to use enticing advertisements. Hence, tremendous amount of commitment is needed on the part of the child & the family to stick with the treating team and their program. Once results start becoming visible, the chance of success of the program increases and also becomes an incentive for other similar children to join in. The secret is to recruit them relatively early & then chances are that more children will be successful. To achieve this, the society should recognize overweight & obesity as major illnesses and mount programs at government & quasi-government levels to increase the awareness in the society and address the problem. This has been and is being done in many parts of the western world. In India we have to start from the beginning and it is better that we do it soon.

## Healthy Eating

In the first 6 months of life, exclusive breastfeeding has achieved excellent results in all parts of the world. Beyond infancy, the child's diet is controlled by the parents. Parents are the ones who buy groceries, cook meals and decide when and where the food is eaten. While shopping for food, right decisions have to be made. Cut back on convenience foods - such as cookies, crackers and prepared meals. Choose more fruits and vegetables. Do not use or strictly limit sweetened beverages. These drinks provide little nutritional value in exchange for their high calories. Limit fast food. Children do follow many of the eating habits of parents. Parents have to be aware of this. Sit down together for family meals - a time to share news & tell stories. Discourage eating in front of TV, computer or video game screen.

## Physical Activity

Physical activity has to be encouraged. This becomes more difficult in small nuclear families. Children should be encouraged to run around and play actively. Even the toys and play material should facilitate activity. Limit TV and recreational computer time.

## Prevention

These measures are for all children.

- Stop snacking while watching TV, computer or mobile.

- Avoid or limit consumption of sugar sweetened beverages.
- Provide plenty of fruits and vegetables.
- Eat meals as a family as often as possible.
- Limit eating out, especially at fast-food restaurants.
- Adjust portion sizes appropriately for age.
- Limit TV and other screen time.
- School based interventions to promote healthy nutrition in children<sup>6</sup>.

Make sure that the child has one health check up visit a year.

## Summary

Is obesity a problem in our society? Yes, probably the most important now. Do we have objective measures to diagnose obesity. Yes - BMI. Is it a problem of adults only. No - it starts in childhood and continues on to adolescence & adults. Which group should we start addressing first. We should start with addressing the problem in children & adolescents and once a healthy life style is built up on them they will continue to be healthy adults and parent healthy children. Where do we start. We should start with programs to increase the awareness of the malady in the society and continue with comprehensive measures at state level, national level and for the world. In many countries they have started with programs in the school

curriculum. Looking at what has been achieved in health care till now, we should be able to eminently correct this global problem. The WILL to do it must come soon in ALL of us and we will be able to eradicate this global malady.

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# 3D BIOPRINTING OF HEART AND BLOOD VESSELS:A NEAR REALITY

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The heart and blood vessels we are born with serve the most important function of supplying blood to every organ of the body. Oxygen, nutrients and essential elements are carried to the tiniest cell and toxic waste elements got rid off, thus ensuring good health for the individual. The cardiovascular system which is made up of the heart and blood vessels functions so precisely, that if anything goes wrong, target organs supplied by the diseased heart or blood vessels are compromised, leading to health problems. Today, doctors diagnose the problem, locate the exact area of the disease process and are able to repair this area, thanks to the development of various natural and artificial substitutes and devices. To name a few, we have childhood defects of the heart such as septal defects being closed with patches, pacemakers helping the heart to beat normally when there is a problem with the electrical conduction, stents implanted to widen diseased and clogged blood vessels and many more. We also have devices which completely take over the function of pumping blood during operations on the heart, thus helping the surgeon to operate on a bloodless organ. Of course, there are certain instances where the surgeon can operate on a beating heart too.

But what happens when the heart totally fails in its function of pumping blood - the condition known as heart failure. Of course, medicines help to a certain extent. Help can be rendered with ventricular assist devices and artificial heart. There is however a limit. What happens when the stented vessel gets narrowed again? After all, medical devices and implants are made up of materials which do have a lifetime. There are also failures because of issues of corrosion of metals, sensitivity to materials, degradability of materials etc. These problems have been reduced to a certain extent by using both materials and living tissue in implants, what we call as tissue engineered implants. Tissue engineering is the technique of taking a material which has properties suitable for a specific use and growing in the laboratory site specific tissues on a material. This construct is then implanted where required. We have liver implants, endothelialized blood vessels (endothelial cells line the inner surface of the heart and blood vessels in the human body) and bone implants with bone cells. The living cells function and help the diseased organ.

The best solution is to replace the diseased vessel or heart or organ with a natural one from a donor. This needs perfect matching between the donor and the recipient and surgery to be done within a certain time frame. To reconstruct a diseased part or an entire organ is a very big challenge. Each organ or tissue however tiny it may be, has a precise geometry suited to its particular function, has precise location of the different cells in the organ and the products they secrete are specific



which either act alone or in conjunction with those of other cells. Recreation of such tissue needs first and foremost an awareness of the structure and the technology to make it in exactly the same way.

Innovation and invention have seen the development of new technologies in the industry from manual processes to two dimensional and now to three dimensional products; medical device technology is not far behind. Industrial manufacturing procedures, particularly in the automobile industry have seen a great transition from use of moulds to the manufacture of various parts to currently, the implementation of three-dimensional technology to develop various products. This has been possible by first creating a design of the object and then using computer technology to build the object layer by layer. The recreated object is complete with all intricate designs and curves. The technologist works on this computerised model till the product is perfect.

Can a similar technology be utilized to recreate a human organ? The medical device industry is not far behind and surgeons and researchers since 1980 have been developing implants made from additive manufacturing (AM) technology otherwise known as rapid prototyping (RP) or three dimensional (3D) printing. The advantage of this is that instead of just mass production of implants of a particular type, the implant can be tailor made to suit a particular patient, *i.e.* an implant which is patient specific.

The process is made possible using this technology along with computerised tomography (CT) scan data. The first step is to take a CT scan of the patient. A narrow beam of X rays is directed to the patient and quickly rotated around the body. The signals that are produced are processed by the computer in the machine and cross sectional images (slices) (tomographic images) of the body are produced. The computer collects a number of these slices and digitally stacks them together to form a three dimensional image of the patient. From this image, the location of basic structures and abnormalities can be identified. This process gives wide scope to make composite, hybrid structures which is so essential in organ substitutes. The geometry, porosity and permeability of such structures are thus controlled and mimic the natural organ. Recent advances in imaging have led to precise image capture. Magnetic resonance imaging (MRI) and micro computerised tomography scan ( $\mu$ -CT scan) provide valuable data in creating these scaffolds. New technologies in segmentation software have also helped in automatic and semiautomatic extraction of surfaces of structures of interest from 3D medical imaging data. The US Food and Administration (FDA) has increased approval under the 510K premarket notification approval system to enable the use of such implants manufactured by 3D printing technology for surgical procedures.

This is just a part of the entire procedure. The next step is the bioprinting of cells onto this structure. Various advanced techniques are today available, such as direct ink printing

(DIW), inkjet printing, laser induced forward transfer (LIFT), stereolithography (SLA) and many others. The first two are commonly used. In DIW, a highly viscous solution or a hydrogel or cell suspension is extruded out to obtain a 3D structure. Inkjet printing is carried out using low viscous solutions like cell suspensions or colloidal solutions are deposited as droplets at high shear rates.

The bioink used to carry out this 3D bioprinting is very important. Its properties are very specific because it has to be compatible with the living cells it carries, it has to be stable and it should have high resolution for perfect printing. This bioink can be a biomaterial with cells where the material degrades and the cells grow and occupy a well-designed space. It can also be only living cells which are printed directly, in a process mimicking normal embryonic growth. The cells grow into new tissues and these are later deposited in a specific pre-designed arrangement and new functional tissue is formed with time. In the former, there is a biomaterial component and a biological component. In the first type, the bioink must have a specific biomaterial as well as biological properties. It should be biodegradable but neither be toxic to the cells nor initiate any immunological response. In a normal tissue, cells are in an extracellular matrix (ECM). Biodegradation should hence match with the tissue it is going to replace, so that as the material degrades, the functional cells can replace the construct with ECM. It also should have correct mechanical properties and be printable. It should have

modifiable functional groups on the surface, so that different biochemical signals or biochemicals could be delivered to the cells. Post-printing maturation should also be proper. It should be compatible with living tissue, and allow cells to live and be active after printing. Further, the bioink should be able to retain the 3D printed structure on its own after printing. Viscosity, surface tension and cross-linking ability are some of the important properties the bioink should have. Its stiffness also is important to allow the cells to live. It should allow cell attachment, growth and proliferation inside the scaffold. Thus, it is understandable how 3D bioprinting differs from 3D printing for industry where biological properties are not important. Hydrogels and more recently polymers have been used as the biomaterials. Natural and synthetic polymers have both been tried, each having their own distinctive advantages and disadvantages in properties.

In the recreation of normal human tissue where first there was tissue engineered implants, now this technology is complimented by 3D bioprinting to produce structures with specific geometrical patterns which are very similar to the normal tissues. To summarise, 3D bioprinting involves layer by layer deposition of biomaterials containing cells in a predesigned architecture to generate functional tissues or an organ. Thus the structure or product is more specifically controlled than in previous methods. Normal tissue being a complex live structure containing different cells in matrix and having an active interplay of secreted molecules, a 3D

bio-printed structure comes closest to tissue or organ from a donor.

Each organ in the human body is unique in the sense that each has a specific physical structure, properties and biological constituents. Pliability of blood vessels is an important property which permits free flow of blood. Diseases bring on changes in this pliability and vessels harden. Blood flowing through these hardened vessels is subjected to various changes in pressure. One thing leads to another and ultimately there is narrowing of the vessel with slowing of blood flow and closure of the lumen. A vessel supplying blood to the heart, if blocked can lead to death of heart tissue supplied by that vessel. Surgical interventions to bypass this block or opening up of the blocked vessel with stents are the usual reparative procedures carried out. A bypass is done using a segment of another vessel from another site in the same patient. Donor site morbidity and re-narrowing of stented blood vessel are some of the problems. Efforts to make blood vessels in the laboratory have led to use of vascular grafts made of different materials which are unseeded or seeded with endothelial cells. Maintaining pliability of such grafts matching that of the host vessel segment which is to be replaced has however been a challenge. Non pliability affects smooth blood flow leading to narrowing and blockage again.

3D bioprinting technique seems to be showing promise in making pliable blood vessels. Recent reports reveal that it is

possible to precisely control certain specific constituents of the bioprinting procedure, enabling parts of the blood vessel structure to be solidified to be harder or softer, while at the same time preserving geometry of the structure.

Making heart tissue is a bigger challenge requiring interplay of so many biological and physical properties. Bioprinting heart tissue requires cardiomyocytes, fibrocytes, endothelial cells, mesenchymal cells, smooth muscle cells and leucocytes. The muscular component of the heart has the functional property of contraction and relaxation for pumping blood from the heart to all the other organs in the body. When diseased, this function is compromised. 3D bioprinting of myocardial tissue using biodegradable scaffolds and cells have been tried. Fast degradation of the scaffold material before the cells are able to grow and function properly, stability and issues of toxicity and immunogenicity of the degradable material are some of the limitations.

Scaffold free 3D bioprinting is the current focus of attention in the development of myocardial tissue. Tissue made by a new technique called microcontact printing for bioprinting has resulted in myocardial tissue having very good anisotropic features which are important for mechanical and electrophysiological properties. Though not yet tested in vivo, it is a big step towards a 3D bio-printed myocardial tissue. Tissue spheroid based 3D bioprinting shows good promise. Tissue spheroids are clusters of cells which if placed close to

each other, fuse together due to surface tension into a living material. This material has the physiological properties of the myocardial tissue. A contractile patch has been made using tissue spheroids of ventricular cardiomyocytes from new born rats, human skin fibroblasts and human coronary artery endothelial cells. The patch was found to be viable after transplantation in rats. There is hence hope.

Advanced techniques for precise deposition of many tissue spheroids have helped in fusing these spheroids together. Human induced pluripotent stem cell- derived cardiomyocytes, fibroblasts and endothelial cells have thus been fused together into cardiac patches. These patches can beat on their own and have throughout the patch, action potential waveforms and uniform electrical conduction as in ventricular muscle cells. When implanted into a rat model the patches were engrafted with new blood vessels, which are positive features of regeneration.

3D bio-printing technology is a boon for the field of organ replacements. With difficulties in obtaining a matched heart for transplantation and long-term problems with diseased blood vessel repair, the possibility of overcoming these obstacles with a 3D bio-printed patient specific organ is something definitely to look forward to in the very near future.

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# GESTATIONAL DIABETES: SPOILER OF THE MOTHERHOOD MOMENT

Surya Ramachandran



Gestational Diabetes is a condition in pregnant mothers wherein high levels of sugar are found in the blood. It usually occurs during the second phase of gestation (24-32 weeks) and disappears post delivery. Those who develop gestational diabetes are at a higher risk of type 2 diabetes mellitus in later life. Children born to such mothers are at a higher risk of being overweight and developing diabetes mellitus. The traditional risk factors for gestational diabetes have been obesity, family history of diabetes mellitus and polycystic ovarian syndrome (PCOS). Standard protocol advised by doctors for prevention is maintaining healthy weight and exercising before pregnancy.

One of the first intervention trials to assess gestational

diabetes, however, states that “first line strategy for preventing gestational diabetes is not working anymore”. The Louisiana State University studied more than 5,000 pregnant women over the past five years. The women took part in clinical trials focused on limiting weight gain in order to prevent gestational diabetes. The moms-to-be improved their diet quality, ate less, and increased their physical activity. They also developed gestational diabetes at about the same rates as the women who didn’t change their diet or activity levels. One of the co-lead authors states “Preventing gestational diabetes is not as simple as reducing weight gain. It may require more individualized approaches based on each person’s risk factors.”

The present five-year study looked at 62 pregnant women with obesity. Nine (15%) developed gestational diabetes. The inability of lifestyle modification to prevent GDM despite successful restriction of weight gain raises the question of whether energy imbalance (energy intake > energy expenditure) is involved in the development or prevention of GDM. In a prospective, observational energy balance study in 62 pregnant women with obesity (BMI > 30 kg/m<sup>2</sup>) the investigators used state-of-the-art methodology to simultaneously measure energy intake and energy expenditure over ~12 weeks starting between 13 and 16 weeks of gestation and concluding between 24 and 27 weeks.

The researchers found that the primary risk factors for gestational diabetes, such as excess fat and insulin resistance, were evident early in pregnancy. Women that developed gestational diabetes were overweight, had higher fasting blood sugar levels and more body fat, particularly around the waist and also had more relatives with diabetes. Some women may develop gestational diabetes because their pancreas doesn't adapt adequately to producing additional insulin to match the increased demand of pregnancy. Others may develop gestational diabetes because their muscles and livers become more insulin resistant.

These findings, however, in no way suggest that pregnant women should abandon their efforts to eat a healthier diet and be physically active. New research is needed into other factors that lead to insulin resistance in pregnancy.

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## 'BLOWING OFF STEAM' BY VIGOROUS EXERCISE INCREASES HEART ATTACK RISK

Sumi S



After a difficult day, several people relieve their stress, frustrations and anger by physical exercise. While regular 'working out' is known to reduce lifetime risk of having a heart attack, vigorous exercise during high emotional negativity is now reported to be harmful. The new report, published in the American Heart Association's journal, *Circulation*, cautions people who when extremely angry or upset 'blows off' their emotional turmoil by exercising. They indicate taxing yourself physically and mentally simultaneously may put you at significant risk for a heart attack.

Dr Andrew Smyth and his research group from the Population Health Research Institute at McMaster University in Canada, conducted the study in more than 12,461 patients with an average age of 58 years. This is a large study including people from 52 countries and ethnicities which provide impressive evidence for the crucial link between mind and body. These patients were recruited in the INTERHEART study after getting a first heart attack. The study staff asked patients if they had been engaged in intense physical exertion or were undergoing extreme emotional issues in the hour leading

up to the heart attack. They also completed a questionnaire about possible disease “triggers” they experienced in the hour before they had a heart attack. Investigators also studied other risk factors such as age, smoking, obesity, high blood pressure and other health problems. The association of heart attacks was highly stronger - over triple the risk for patients who said they had been extremely angry or upset and hence engaged in heavy physical exertion.

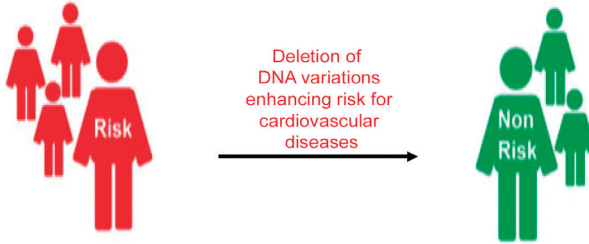
Intense physical exertion or extreme anger can individually trigger a heart attack, but the risk may be highest if the two are combined, according to this new study. The lead author Dr Smyth describes that both triggers can raise blood pressure and heart rate. This can change blood flow through blood vessels and reduce blood supply to the heart. This is more prominent in blood vessels already narrowed by plaque. Investigators hence recommend that a person who is angry or upset and who wants to exercise for stress relieving, not to go for extreme activity. The authors acknowledge that the definition of emotional negativity and extreme physical exertion differ from person to person. The authors recommend that when you are in a negative emotional state, it is better to avoid combining extremes of what is unusual for you. Working out is the best way to have a healthy heart, yet do not try to outdo your hardest workout as a way to release energy and aggression after a particularly stressful event.

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# MYSTERIOUS DNA REGIONS AND HEART DISEASE RISK

Vikas Kumar



*Credit: Baldwin lab/Scripps Research*

Billions of people in their genome carry unidentifiable gene sequences which increase the risk for development and progression of heart attack, high blood pressure, bursting or blockage of blood vessels etc. irrespective of their diet, occupation, exercise or medical therapy.

Recently researchers from Scripps Research Institute discovered that deletion of deleterious DNA sequences from the genome stopped blood vessel abnormalities associated with these diseases.

The authors of this study revealed that more than one-third of all genes known to regulate heart disease contain these wicked DNA sequences and thus could be explored as newer targets for treatment of blood vessel related diseases. They identified DNA sequences designated as 9p21.3, the genetic determinants of cardiovascular risk, cause abnormalities in smooth muscle cells in the wall of blood vessels and

thus impairs blood vessel contraction and relaxation. The abnormal smooth muscle cells increases risk for clogging of blood vessels and thereby lead to heart attacks and stroke (lack of blood supply to the brain).

For more than a decade, it is well known that 9p21.3 sequences are genetic determinants for risk of cardiovascular disease but what causes this risk was unknown. The current study suggests that 9p21.3 determines the stability and optimal function of smooth muscle cells of blood vessels and provides a newer target for the treatment of blood vessel diseases.

According to a WHO report, cardiovascular diseases especially those affecting the heart and blood vessels result in more than 18 million deaths worldwide. These diseases stem from the building of plaque or clogging of blood vessels (atherosclerosis) which leads to heart attacks. Risk factors for cardiovascular diseases include physical inactivity, smoking, obesity, high cholesterol and high blood pressure. Researchers have also identified several genetic determinants of cardiovascular disease risk. The 9p21.3 haplotype was one of the first identified DNA region associated with risk of cardiovascular diseases. Several studies have reported an association of this DNA region with risk for development of advanced heart and blood vessel diseases. The precise mechanisms or molecular basis for the development of blood vessel abnormalities in individuals having this DNA region were unknown. A major hurdle associated with studies on the disease risk DNA region is that it is found only in humans and poorly resembles DNA regions in animals. This DNA region does not anchor protein-coding genes; so its function is unknown. The nonprotein-

coding DNA region was earlier described as “gene desert or junk DNA” and thus was ignored in research by most of the scientists. Recent studies using DNA sequencing techniques unravelled their association with various diseases.

Baldwin and her team, the authors of this study wanted to address the role of this DNA region on development and function of blood vessels. For this purpose, authors wanted to develop blood vessel cells in a dish and then interrogate them using advanced DNA editing techniques. The authors collected blood from people who had either high risk or low-risk DNA variations and then generated induced stem cells. The risk-prone DNA sequences from induced stem cells were then removed using advanced genetic techniques (TALE nucleases). Induced stem cells were then transformed using advanced bioengineering and gene profiling methods into smooth muscle cells of blood vessels.

Researchers at Scripps found that more than 3000 thousand genes (approximately 10% of the total human genes) were affected in cells derived from high-risk individuals. Deeper examinations using a high-resolution microscope revealed that cells with risky DNA variations had decreased contractility and had lesser ability to attach to surroundings than cells with low-risk DNA variations. Researchers from the Scripps Research Institute questioned whether these altered genes influence well-known genes linked to heart disease. Surprisingly, more than a 1/3rd of these genes were altered suggesting that this risky DNA variation/9p21.3 haplotype regulates heart disease genes.



Further investigations revealed that cells derived from individuals with risky DNA variations have higher levels of another master regulator genes called ANRIL, which do not make proteins. When healthy cells were introduced with ANRIL DNA regions using gene editing techniques, healthy cells developed disease related properties. These results confirm that ANRIL DNA sequences act as conductors for switching off healthy and disease prone state in smooth muscle cells of blood vessels.

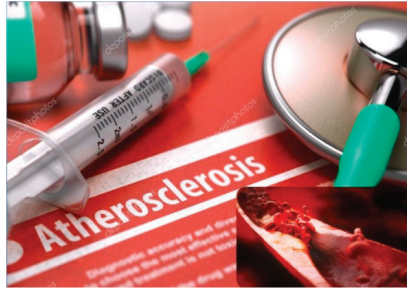
In conclusion, gene deserts are not deserts anymore but carry useful information associated with human physiology. DNA deserts or junk DNA are unique DNA regions carrying information associated with heart diseases. Targeting the risky DNA variations using advanced DNA editing techniques could be a new therapeutic approach for heart and blood vessel diseases. High-risk individuals carrying 9p21.3 haplotype have thus impaired blood vessel development and function leading to development of heart diseases. This study also indicates the wide applicability of advanced gene editing techniques for studying human diseases.

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# THE BEGINNING OF A NEW HISTORY

Jayalekshmi V S



*Photo courtesy: Tashatuvango*

A healthy society is always a wealth for a nation. People's aspirations and desires cannot be met without longer, healthier and happy lives. Communicable diseases have always been a threat to the society seizing thousands of lives per year, hence forcing the healthcare industry to grow to eradicate the diseases. According to the World Health Organization (WHO), vaccination, one of the major diseases preventing strategy averts 2.3 million deaths per year in all age groups. Vaccination stimulates an individual's immune system by administering an antigenic material against the pathogen. It is believed that the tradition of vaccination may have originated in India in AD 1000. Textual evidence was given by the French scholar *Henri Marie Husson* in the journal *Dictionaire des sciences médicales* on the method of inoculation described in the *Sact'eya Grantham*, an Ayurvedic text. It was Edward Jenner, a doctor in Berkeley who initiated vaccination of the

modern era. Jenner's vaccination led to preventive strategies for several dangerous communicable diseases.

21<sup>st</sup> century saw the emergence of a new category of diseases called as "diseases of civilization" because of the contribution of modern diet and lifestyle to the causation of these diseases. Atherosclerosis is one among them where arteries are blocked due to the buildup of low density (LDL) cholesterol named as 'bad cholesterol'. At present, drugs such as statins are used to lower LDL cholesterol which has to be taken on a daily basis. These drugs have adverse side effects. The second line of treatment of using monoclonal antibodies targeting PCSK9, which plays a role in preventing clearance of lowdensity lipoprotein cholesterol from the blood, is highly effective, but their effect is also short-lived, and the drug is expensive. These challenges in therapy encouraged a group of researchers led by *Christine Landlinger* from Austria and Netherlands to create a vaccine against atherosclerosis keeping aside the difficulties and risks of development of a vaccine against a multifactorial chronic disease. The study published in *European Heart Journal*, is the first to show that genetically modified mice immunized with an endogenous protein can trigger the immune system to produce antibodies. They developed AT04A vaccine containing short peptides termed as AFFITOPes against PCSK9 protein inducing antibody production. When AT04A vaccine was injected under the skin in mice that have been fed a fatty, western-style diet in order to induce high blood cholesterol levels and development of atherosclerosis, it reduced the total amount

of blood cholesterol levels by 53% and inflammatory markers by 21-28% compared to unvaccinated mice. Moreover, the antibodies produced were functional over the whole study period and concentrations were stably high till the end of the study. Indeed, there is the question: “How safe it is?” Safety, the response in humans and the unknown long-term side effects are to be very carefully addressed. Hence in 2015, a phase I clinical study was started at the Department of Clinical Pharmacology, Medical University of Vienna, Austria, studying AT04A and another molecule AT06A in 72 healthy individuals. The study is expected to be completed at the end of this year.

Developing a vaccine against atherosclerosis is a revolutionary approach in the history of chronic diseases. If these findings in mice model translate successfully into humans, this would result in an effective and more convenient treatment for atherosclerosis. Moreover, this may open up a new therapeutic approach against all multifactorial chronic diseases.

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# HEART HEALTH WITH SOYA BEANS

Ciji Varghese



The soya beans are part of the legume family, grows in pods enclosing edible seeds. The key benefits of soya are its high protein content, vitamins, minerals and fibre. The high fibre content makes soya containing foods valuable in cases of constipation, high cholesterol and type-2-diabetes. Soya beans are rich in various bioactive plant compounds. Of all the phytonutrients in soya beans, the Isoflavones are worth mentioning due to its antioxidant property. Daidzein and Genistein are the isoflavones called as the plant estrogens (phytoestrogens) and have been found to have beneficial role in heart health. FDA recommended intake of soy protein is around 25-30g/day.

Replacing high fat animal foods and dairy products with soy foods can be heart healthy. Soy milk is effective in preventing the increase in serum levels of total cholesterol and LDLc. As

we know, the antioxidants prevent or repair the cell damage that free radicals cause including damage to the innermost layer of the arteries. The soy foods help lower the risk of heart attacks by preventing the formation of plaque (it is made up of fat, cholesterol, calcium and other substances found in the blood) in the arteries and oxidation of LDL cholesterol.

According to Russica *et al*, the inclusion of whole soy foods in a lipid lowering diet significantly improved the plasma lipid profile indicating the effective approaches for the management of primary cardiovascular disease risks. All these risk factors can be a consequence of dietary habits and may therefore be influenced by diet and life style modifications. The soya bean has been transformed into a number of popular soya based foods like Miso, Tempeh, and Tofu etc. It is an excellent source of the minerals calcium and Iron. Consumption of soy foods can help in lowering the serum cholesterol, and the fiber content in soybeans can work towards decreasing the absorption of cholesterol in the biological system. It is because of these benefits soybeans are considered to be heart- friendly and this heart healthy food also adds protein, fibre and variety to the diet.

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