Member: International Committee of Diabetes Magazines, International Diabetes Federation (IDF)

ISSN 1908-1227

diabetes philippines WATCH

A Publication of Diabetes Philippines

May - December 2015

Year MMXV, NO.2

DP 2015: THE YEAR THAT WAS

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Use of Oral Hypoglycemic Agents during Pregnancy

Meet Chesca: IDF Youth Leader

Living with Type 1 Diabetes

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REFERENCES: 1. Haak T, Meinicke T, Jones R, et al. Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diab Obes Met. 2012; 14: 565-574. 2. Price computed based on Trajenta and Trajenta Duo treatment cost per day (using list price for both brands)
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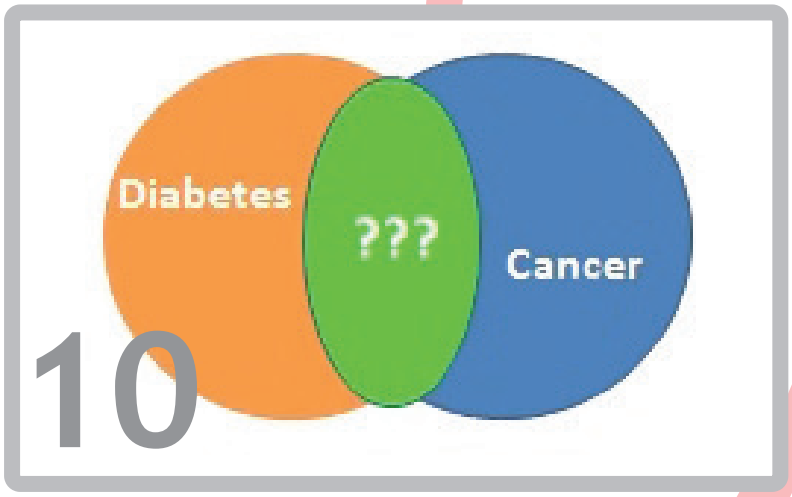
REGULARS



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2015 was a fruitful year for Diabetes Philippines. We were able to hold workshops and fora in areas not previously reached by the organization. Our annual convention was immensely successful. Our World Diabetes Day 2015 celebration, together with the launch of the " Tara na, Stop Diabetes" campaign on social media, was able to reach thousands of people.

As mentioned earlier, our educational activities were done in areas not commonly reached by the continuing medical education programs. The logistics, like going via the roll-on/roll-off (RORO) ship, initially posed some challenges. Nevertheless, we still determined to reach the far-flung regions of Occidental Mindoro and address our underserved "kababayans" thirst for knowledge on diabetes. The workshops and fora were all well attended. They were very rewarding for the educators themselves. Take time to read the contributed articles of the Tamaraw Diabetes Club and of Dr. Ma. Teresa Tan to get a feel of what it was like for those involved in the Mindoro chapter.

The 32nd annual convention exceeded our expectations with an all time high number of attendees. This is evidence enough that Diabetes is a growing major concern for medical practitioners and allied healthcare professionals alike, and that more CME updates are needed. Likewise, the quality of the talks given was high-level. In this issue, we included summaries of some of the lectures, such as the concept of metabolic inflexibility, diabetes and cancer and the cardiovascular impact of maternal diabetes on the fetus.

2015 was the year Diabetes Philippines got into social media. Our campaign for diabetes prevention, "Tara na, Stop Diabetes" was launched with a video on facebook for World Diabetes Day. This was followed by a call to action to join us in the "Stop Diabetes" hand wave movement. Our very able member of the board, Dr Fatma Ibba-Tiu spearheaded the said campaign. It is still on going and has been well received by the public - with thousands of likes and shares - so far.

2016 for Diabetes Philippines promises to be another great year. We will continue to take on the challenge of "Tara na, Stop Diabetes" and will step up our efforts to address this. To quote what Dr. Shin Young-soo, the WHO regional director for Western Pacific, said during the World Health Day 2016 program (with the theme-Beat Diabetes), "Let us work together in the forefront against Diabetes. Get into the (blue diabetes) circle with us".

Dr. Rima T. Tan
President

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The prime mover of effective prevention and excellent diabetes care in the Philippines

OUR VISION

By 2020, we envision:
1. Fewer Filipinos with diabetes
2. Improved quality of life for Filipinos with diabetes

OUR VALUES

INTEGRITY *Above all, the nobility of our purpose.*
We serve patients, pursue education and conduct research with zeal and without regard for personal gain. Honesty and transparency rule our behavior in relating with fellow members, partners, supporters and other stakeholders of our organization.

EXCELLENCE *Passionate workers, we expect from ourselves only the best effort.*
We continuously upgrade our knowledge and skills, adopt ever-improving technologies, and expand the reach of our services to attain our vision. Our mentors, generous with their knowledge and time, model excellent leadership.

COOPERATION *We work as one for the common good, enjoying the camaraderie, observing respect and maintaining loyalty even in dissent. We partner with institutions and other specialties that aim for the same goal. Caring for everyone's well being, we make work pleasant for members and staff.*

COMMITMENT *Persistent in our search for solution to diabete. We have selflessly devoted five decades to the improvement of diabetes care, education and research to prevent the onset of the disease in high risk individuals and the complications in those already afflicted by it. We take on responsibilities with diligence until their successful conclusion.*

Greetings for a new year!

In this volume of ***Diabetes Watch***, we are featuring the organization's activities and highlights for the past year. 2015 was a particularly busy year for DP. The year brought us to far reaching places for the 3 diabetes workshops and lay fora – traveling to the northern and southern regions of Occidental Mindoro and to the paradise island of Bohol. The 32nd annual convention last November with the theme ***#diabetes trends*** was attended by a record number 1061 delegates. Here, we provide a recap of some of the scientific lectures during the convention. Aside from the plenary and breakout sessions, this year's annual convention was also the venue for the launch of the *"TARA NA, Stop Diabetes Campaign"*, DP's diabetes prevention strategy to promote awareness in social media. The fellowship night culminated with the awarding of the winner of the jingle-writing contest with the theme *Awit Tamis - Iwas Diabetes*. *"Matamis ang Buhay"* was chosen from among 12 submitted entries. The day after the convention was spent at the Pasig City sports complex for *Gimik Diabetes*, DP's World Diabetes Day celebration. The year 2015 ended with DP Philippines' participation in the IDF's World Diabetes Congress in Vancouver, Canada. Officers and members of Diabetes Philippines clad in native shawls congregated at the Global Diabetes Village for the presentation.

In this issue, we introduce our IDF young leader in diabetes, Chesca Villanueva. Addressing the special considerations of our young diabetic patients remains one of the unmet needs in the treatment of diabetes. So we decided to chat with some of our type 1 patients. Jamie, Paul and Gina provided their perspective – on their lives, how they cope and what activities can help address their needs.

2015 was a fruitful year indeed. Join us for more fun-filled educational activities in 2016!!

Marsha C. Tolentino, MD
Editor-in-Chief

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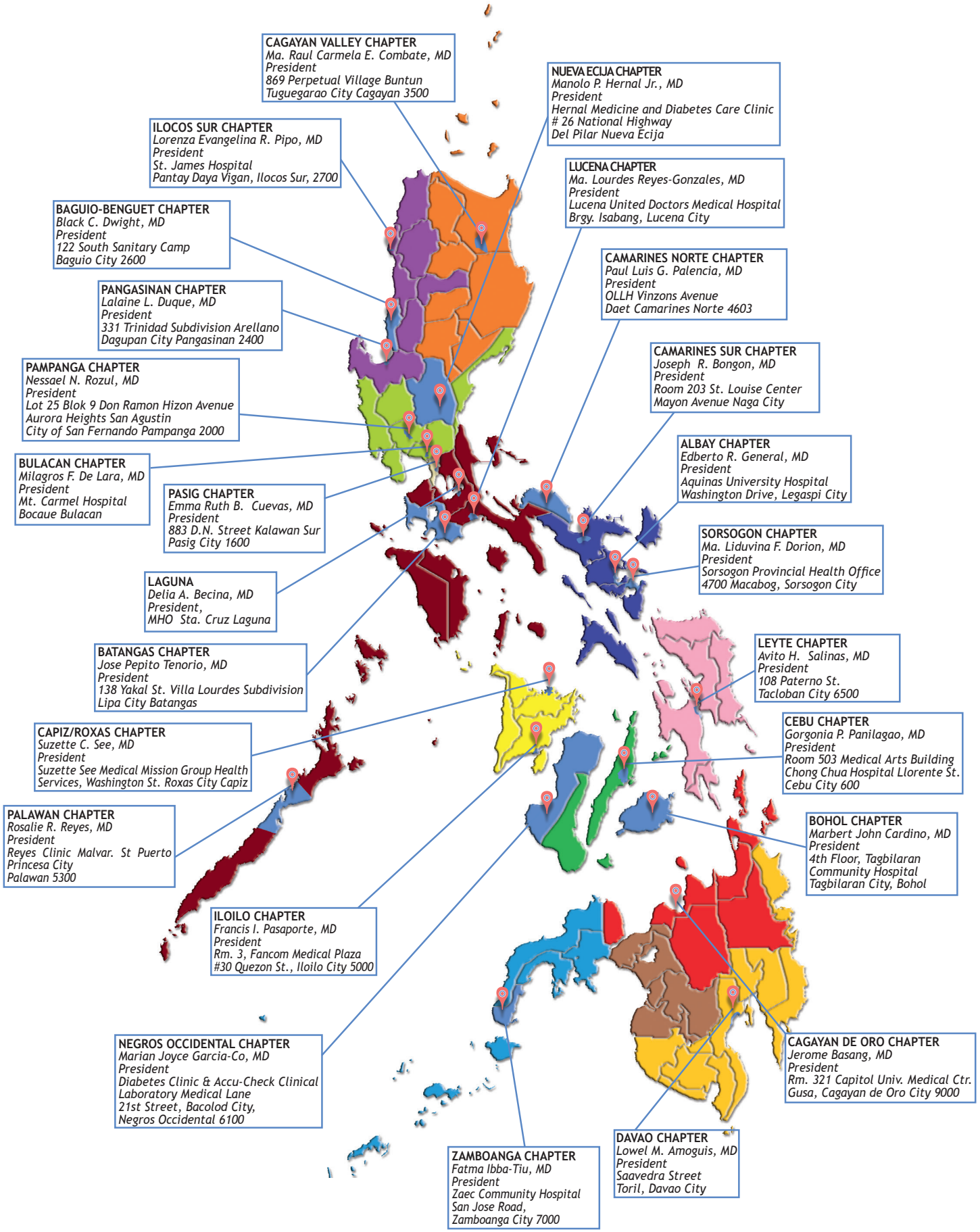

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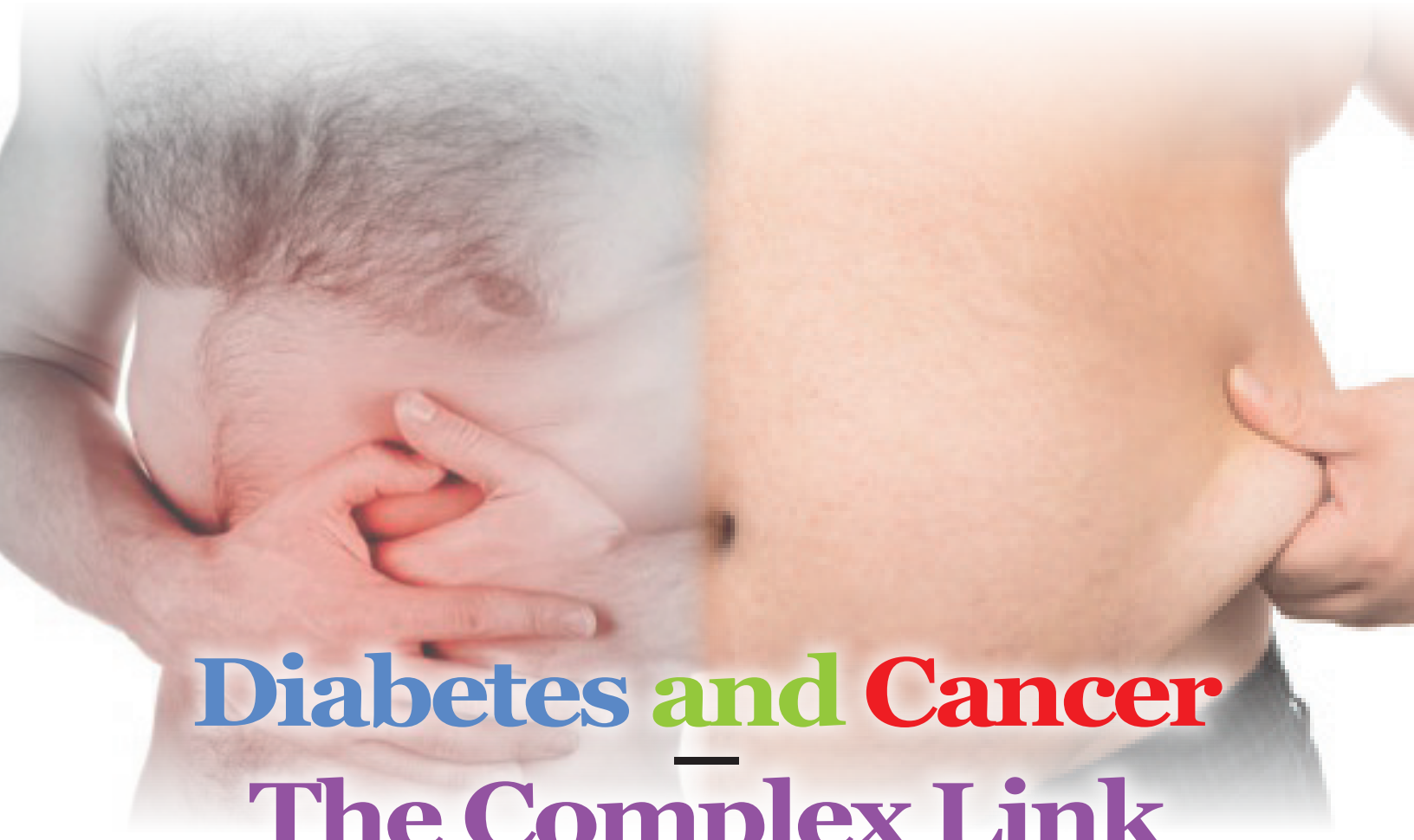


Diabetes and Cancer — The Complex Link

Denky Joshi W. Dela Rosa, MD, FPCP, FPSMO

A new class of drugs for cancer is called targeted therapy. They are different from traditional chemotherapy not because they only affect cancer cells without causing damage to normal cells but because they act on specific molecular targets that affect the ability of cancer cells to survive. Chemotherapy, on the other hand, acts mostly on the DNA and other cellular processes that are involved in cell replication. Some targeted drugs have totally altered the natural course of certain cancers such as kidney and lung cancer.

The molecular link between diabetes and cancer lie in the processes involved in cell signaling. Targeted therapies affect cellular signaling which allows different molecules to interact with one another to promote the growth and survival of cancer cells. There are thousands of these signaling pathways in the body and insulin together with insulin-like growth factor (IGF) form part of these pathways. Hyperinsulinemia may cause a diversion of the signaling pathway from a primarily metabolic to a mitogenic pathway.

Another potential effect of insulin is that it reduces the levels of sex hormone binding globulin which in essence increases the amount of free estrogen. High levels of free estrogen may be a risk factor for postmenopausal breast cancer.

Aside from involvement of insulin and similar growth factors, it is also possible that the chronic, low grade inflammation brought about by diabetes may be responsible for the beginnings of cancer.

Mechanism versus Epidemiology

Even if there are mechanistic relationships between diabetes and cancer, not all types of cancers are increased among diabetic patients. Many individual studies have claimed an increased risk of many types of cancer among patients with diabetes but the strongest evidence of association is found between diabetes and breast, endometrial, colon and intrahepatic cholangiocarcinoma. On the other hand, a negative association between diabetes and prostate cancer is seen. Patients with diabetes have a low-

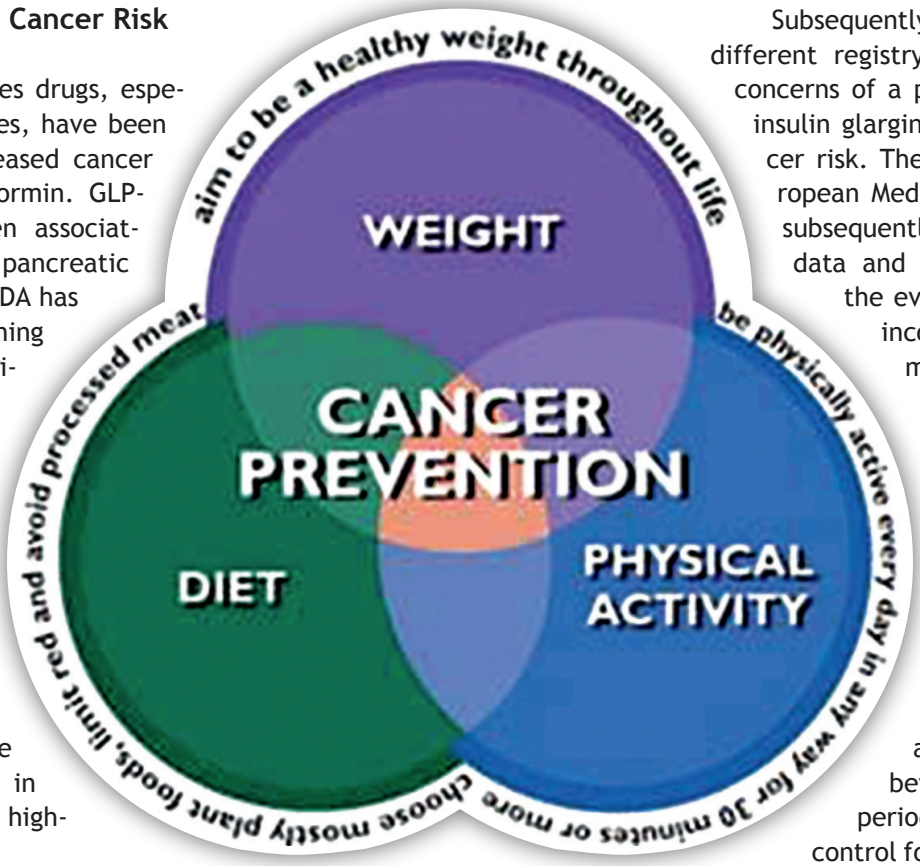
er risk of developing prostate cancer.

Cancer and diabetes have common lifestyle risk factors such as obesity, sedentariness and poor diet. (Source: www. aicr.org)

Apart from potentially increasing cancer risk, the presence of diabetes may also have a negative impact on certain cancer outcomes. The prognosis of some diabetic patients with cancer may be adversely affected due to the inability to administer full dose treatment or delays in treatment due to higher rates of complications.

Diabetes drugs and Cancer Risk

Almost all diabetes drugs, especially insulin analogues, have been associated with increased cancer risk except for Metformin. GLP-1 agonists have been associated with thyroid and pancreatic cancer risk. The US FDA has issued a safety warning regarding the use of Pioglitazone and bladder cancer risk. It says that although there was no overall increased risk of bladder cancer with pioglitazone use, an increased risk of bladder cancer was noted among patients with the longest exposure and in those exposed to the highest cumulative dose.



Some observational studies have linked sulfonylureas to a higher overall risk of developing cancer but none are randomized controlled trials and the results of these different observational studies bear no consistency in pointing to an association.

Regarding Metformin, no trial is available which shows that it may increase cancer risk. There are even studies that show that Metformin may be associated with reduced cancer risk. Some studies have shown that its use may improve cancer outcomes. These results however, come from observational studies. In my opinion, given that these are the best evidence available and since Metformin is quite tolerable for many patients, we should take advantage of every opportunity we have to incorporate this drug into our patients' diabetes regimen.

Insulin Analogues and their Mitogenic Potential

The insulin analogues have been the most controversial diabetes drugs linked to cancer risk particularly insulin glargine. Initially, molecular studies have linked the mitogenic potential of insulin analogues with their IGF receptor affinity. Insulin glargine was shown to have 6-8 fold higher affinity to the IGF-1 receptor than human insulin.

Subsequently, there were four different registry studies that raised concerns of a possible link between insulin glargine and increased cancer risk. The US FDA and the European Medicines Agency or EMA subsequently evaluated these data and both concluded that the evidence presented are inconclusive because of methodological limitations. Cited reasons for these limitations are: short follow-up, limited information on patient's use of insulin products, unable to account whether the patients used any anti-diabetic drugs before the study time period and the inability to control for confounding factors such as obesity, smoking and family history of cancer.

What are the implications of these data on how I manage patients?

Even when data are mostly observational, a pattern is trending for a relationship between diabetes and breast, colorectal and endometrial cancers.

Breast and colon cancers are in the top 5 causes of cancer and many of these patients come in with relatively early stage disease and therefore, still have a long survival ahead. Part of what I monitor during the course of

treatment and survivorship is blood sugar, whether or not these patients who came in are diabetic at the time of initial consult. For those patients who are already diabetic, I clearly explain to them the importance of controlling blood sugar and its possible effect on outcome. I tell them that when a patient's blood sugar is high, it creates an environment in the body which acts like a fertilizer to the tumor.

It is a very common phenomenon among breast cancer survivors to gain weight post-treatment whether or not they have undergone chemotherapy and the same can also be true for colon cancer patients. Weight gain after cancer diagnosis can adversely affect prognosis among breast and colorectal cancer patients regardless of whether they have diabetes or not.

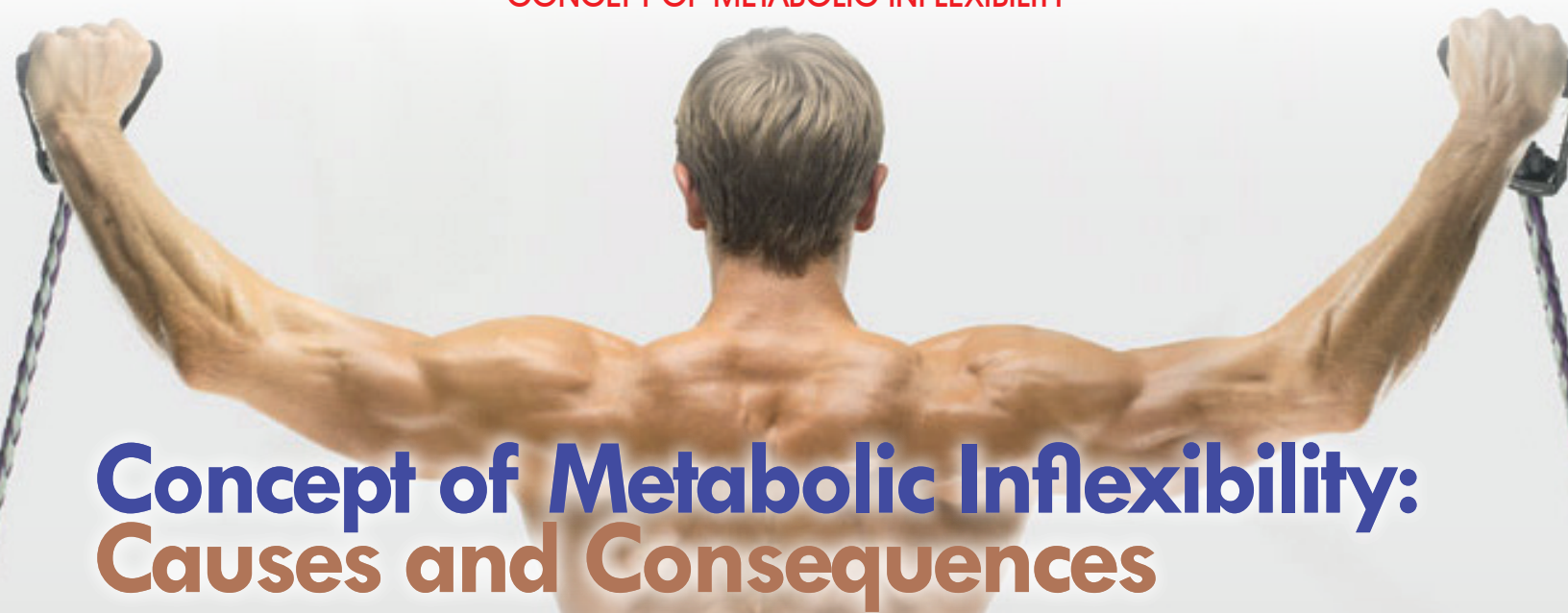
I also encourage patients to engage in regular physical activity and explain to them that this affects hormone balance which is important for breast cancer. There are also studies that link physical activity with better survival for colorectal and breast cancer.

Apart from its potential effect on prognosis for cancer patients, another benefit of controlling blood sugar has to do with its additional burden on the heart. Patients with breast cancer often receive doxorubicin which is known to be cardiotoxic and some of them receive radiation as well.

If the patient's breast cancer is on the left and she undergoes radiation, even with modern radiation techniques, the heart is bound to receive a certain dose of radiation and this will have an impact on the cardiovascular health of the patient. So if the patient has diabetes, received doxorubicin containing chemotherapy and radiation therapy to the chest on the left side, this is a triple whammy on the patient and her cardiovascular risk may increase exponentially.

Conclusion:

With regards to diabetes medications and cancer, data have been inconsistent, confusing and tainted with many biases. At this time, there is no clear correlation between the use of diabetes medications and cancer. In the absence of such clear and consistent correlation, we need to manage uncontrolled diabetes because the correlation of diabetes, cerebrovascular, cardiovascular, and other target organ damage as well as cancer is stronger than the correlation between diabetic medications and cancer. We cannot let our fear of our patients developing cancer dominate the immense likelihood that they will suffer heart attacks, strokes, kidney failure and blindness which are far more likely to happen. There are screening programs for cancer that we can employ. But we also have to be more thoughtful in our choice of medications for diabetes bearing in mind the personal and family history of the patient. Lastly, should your patients develop cancer, I am always just around the corner to refer your patients to.



Concept of Metabolic Inflexibility: Causes and Consequences

Ernesto L. Ang, MD, MS, FPCP, FPSD

Humans have a constant requirement for energy. However, humans only eat intermittently. To cope with the discontinuities in the supply of energy, our normal physiologic organs respond to blood nutrients through a series of well-controlled mechanisms. Energy is stored at time of surplus (during fed state), glucose is stored as glycogen in the liver and skeletal muscles, and triglycerides is deposited from fatty acids mainly in the adipocytes. This stored fuel is released at times of requirement during the fasting state from glycogen to glucose and triglyceride to fatty acids.

It's amazing to know that the human body can switch from one fuel to another during the cycle of fasting and fed states. This is because our organs are "metabolically flexible". Flexible in a sense that it preferentially oxidizes FAT in times of shortage (fasting) & preferentially oxidizes carbohydrate (CHO) in time of plenty (after a meal). Metabolic inflexibility is a decrease or loss of metabolic flexibility and this impairs the capability of skeletal muscle to modulate between glucose and lipid oxidation. Metabolic inflexibility is hypothesized to play a role in various disease processes such as insulin resistance state, obesity and Type 2 diabetes.

In the clinic, metabolic flexibility is measured by comparing the volume of oxygen consumed to the volume of carbon dioxide produced during the process of cellular metabolism. Respiratory quotient (RQ) is the ratio of CO2 produced to O2 consumed while food (substrate) is being metabolized and is measured through indirect calorimetry.

An RQ of 0.07 indicates that fat is the predominant fuel source, RQ of 0.85 suggests a mix of fat and carbohydrates, and a value of 1.00 or above is indicative of carbohydrate being the predominant fuel source. (see table 1)

How do we use RQ to evaluate metabolic flexibility in an individual?

Availability and the ability to utilize energy dramatically change over time. We can be sleeping or sprinting, eating or fasting. Our ability to adapt to these conditions depends greatly on the ability of our individual cells (particularly our muscle) to be metabolically flexible. For example:

- When we ingest FAT, metabolic flexibility helps us oxidize the fat instead of storing it so our RQ should be ***LOW***.
- When we ingest carbohydrate, metabolic flexibility helps us control blood glucose by oxidizing glucose instead of fat, so our RQ should be ***HIGH***.
- When we fast, metabolic flexibility helps us oxidize the fat stored (triglyceride in the adiposcytes), instead of starving for sugar or developing low energy, so our RQ should be ***LOW***.
- When we exercivse, metabolic flexibility allow us to oxidize more stored fat and produce more energy at

Respiratory Substrate	RQ value
Glucose	1.0
Fatty acid	0.7
Protein	0.9

Table 1: The following table shows the RQ values for different classes of respiratory substrate when they are used for aerobic respiration.

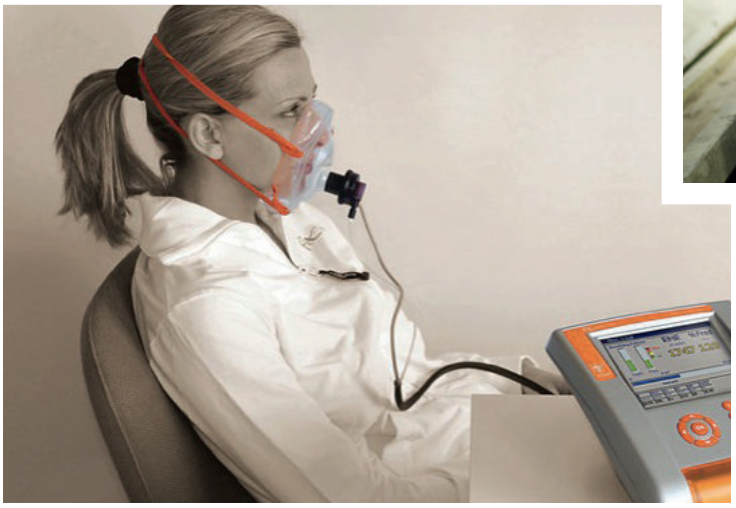
all levels of effort, so our RQ should be ***LOW***.

Consequences and clinical implication when metabolic flexibility is impaired

When metabolic flexibility is impaired, our cells cannot easily switch fuel sources. This leaves us unable to respond well to changing conditions. When we ingest carbohydrate, we cannot dispose of blood glucose as rapidly as we should. This results in poor glycemic control or wide blood sugar swings. During fasting our ability to oxidize fat is diminished and this lead to continual demand for glucose, even at rest. Fasting makes us hungry more rapidly and become catabolic more rapidly.

Therefore, a metabolically inflexible person trying to reduce food intake is also likely to reduce their metabolic rate and during exercise the ability to oxidize their own fat decreases, and their demand for glucose increases. The ultimate result is an insulin resistant state that may leads to Type 2 diabetes, which is commonly a consequence of obesity.

The exact mechanism as to the cause of metabolic inflexibility in the skeletal muscle is unclear but there are several factors that contribute to its development namely: genetics, environmental factor, physical inactivity and excessive calorie intake. On a cellular level, abundant evidence points to the reduced fatty acid oxidation in the mitochondria. The mismatch between oxidation and uptake (seen in excess fat intake) results in increased level of intra-myocellular triglycerides (IMTG) and ceramide, which interact with insulin signaling and reduce insulin glucose uptake leading to insulin resistance.



In terms of prevention and restoring metabolic inflexibility, studies have shown that both exercise and weight reduction have some benefit. Moderate weight reduction as a result of dietary modification or large amounts of weight loss by surgery intervention consistently improved insulin sensitivity. However, despite improved insulin sensitivity there is lack of improvement in skeletal muscle fatty acid oxidation. Regular physical exercise not only improves insulin sensitivity but also improves capacity of skeletal muscle to utilize fatty acids during exercise, improve fasting fat oxidation therefore, improve metabolic flexibility.

In summary: Metabolic flexibility is the ability of our organs to switch back and forth between two major energy substrates—GLUCOSE and FATTY ACIDS. Metabolic flexibility allows us to control blood glucose following a meal, oxidize our stored fat during fasting and respond appropriately to changing energy supply and demand. Metabolic flexibility is measured via changes in respiratory quotients (RQ), which approximate the ratio of carbohydrate to fat that our bodies are burning during the time period measured. Metabolic inflexibility begins as impaired fatty acid oxidation at the mitochondrial level and this contributes to obesity, insulin resistance state and Type 2 diabetes. Weight reduction improves insulin resistance. Therefore combined weight loss and regular exercise is effective in restoring metabolic inflexibility since exercise can restore our ability to oxidize fat.

WHO HAS DIABETES?

Dr. Richard Elwyn Fernando

Who has diabetes?

Do you have diabetes? Do I have diabetes?

In a group of people, it is not easy to simply identify those who have diabetes and those who do not. Frequently, there are no signs nor symptoms of the condition. The more frequent type 2 diabetes creeps in very slowly and insidiously that many of the affected individuals really feel nothing abnormal at all... at least at first. Years later they may experience peeing frequently, drinking gallons of water a day and noticeably losing significant body weight in spite of a horrendous appetite. Failure to identify and treat these persons allows them to develop debilitating or even fatal diabetes complications. The very infrequent type 1 diabetes comes in more dramatically at early ages with noticeable symptoms usually before they turn into their teens. They may also develop the different complications of diabetes.

Identifying any individual who has diabetes is therefore a serious matter. Anyone who has diabetes understands that the diagnosis carries the stigma of a lifetime condition. Imagine having a condition that is undeniably progressive even when properly controlled. Keeping track of nutrition, exercise, medication and clinic follow-ups require discipline and diligence. Having diabetes may require changes in lifestyle and may also involve other members of the family.
These are all necessary for a long fulfilled life even with diabetes, but with little or no complication.

Diabetes is a laboratory diagnosis. Any person suspected of having diabetes must undergo a blood sugar test. Because of its growing burden, suspect diabetes in individuals who have family members with diabetes, those who are overweight and do not exercise at all, those who have reached 40 years and above, and Asians including and emphasizing us Filipinos. Other suspects are those with elevated blood sugars, blood pressure, and/or blood fats/cholesterol. Those who have had heart attack or brain attack/stroke, including women who had glucose abnormalities related to pregnancy, are all suspects and should undergo blood sugar testing. The presence of these risk factors increases the likelihood of having diabetes in the present or in the future.

The most common test is called fasting blood sugar (FBS). Since the sugar that is being tested in the blood is glucose, it is also called fasting blood glucose and the terms sugar and glucose are interchangeable. Blood is drawn 8 to 10 hours after the last meal (max 12 hours). It is standard to take it in the morning before breakfast. Other than water, oral intake of anything may unfavorably

affect the test. It is advised to repeat the test after a week or so to verify positive results.

FBS values below 100 mg/dl are classified as normal. Values above 125 mg/dl welcomes the individual to the diabetes club membership. Results that fall from 100 to 125 mg/dl, the grey area, have prediabetes and are on their way to full time diabetes in a short time without intervention. Practicing a healthy lifestyle best prevents conversion from prediabetes to overt diabetes. High risk individuals should have their FBS every year.

In the presence of symptoms (frequent urination, excessive thirst and weight loss), there is no need to do a blood sugar test after fasting. A random or casual blood sugar test (RBS) suffices in these individuals. Normal RBS values are below 140 mg/dl. It will be above 200 mg/dl if one has diabetes. Prediabetic RBS values are from 140 to 200 mg/dl.

Prediabetes usually requires verification using a tedious test called OGTT (oral glucose tolerance test). In this examination, the individual with prediabetes is tested for FBS. 75 grams of glucose is dissolved in a glass of water (some add calamansi or lemon for flavor) which the individual takes orally within 5 minutes. Some laboratory centers have commercially prepared 75 grams glucose drink with more appealing flavors. They work just fine. Blood is tested again for sugar after an hour and after 2 hours. In a normal individual, FBS is always below 100mg% and there is no value above 140mg% after the drink. In people with diabetes, FBS is above 125mg% and/or blood sugar after the drink goes beyond 200mg%. Any result considered not normal and not yet diabetes is categorized as prediabetes.

Advanced countries like the United States have a standardized blood sugar test called glycated hemoglobin. It reflects the blood sugar fluctuations for the past two to three months. This test does not require fasting and is also called glycosylated hemoglobin, hemoglobin A1c, HbA1c or simply A1c. Values below 5.5% are normal while values above 6.5% confers diabetes. Values from 5.5% to 6.5% is prediabetes. While this test is available in the Philippines, there is no program yet to have it standardized. It is therefore not standardized here and is not recommended to be used for the diagnosis of diabetes in our country. It is best used for monitoring control of blood sugar among individuals with diabetes.

There you are – all the values you need to identify normal, prediabetes and diabetes using FBS in high risk asymptomatic persons or RBS in symptomatic individuals. And then there's the gold standard called OGTT and the not so golden A1c. If you are at risk of getting diabetes, do a yearly FBS and be sure to report to your doctor even if you can interpret the results yourself. Your doctor's advice may include other issues which can be overlooked by one test. But be an advocate and convince other high risk individuals to be tested. Next to diabetes prevention, early diagnosis and treatment best prevents diabetes complications. Do not forget the old saying: "He who knows that the soup is hot and does not tell his neighbor is not an honest man." Go and be a blessing to others.

CARDIOVASCULAR IMPACT OF MATERNAL DIABETES ON THE FETUS

Maria Raquel M. Pasimio, MD, FAAP, DPPS

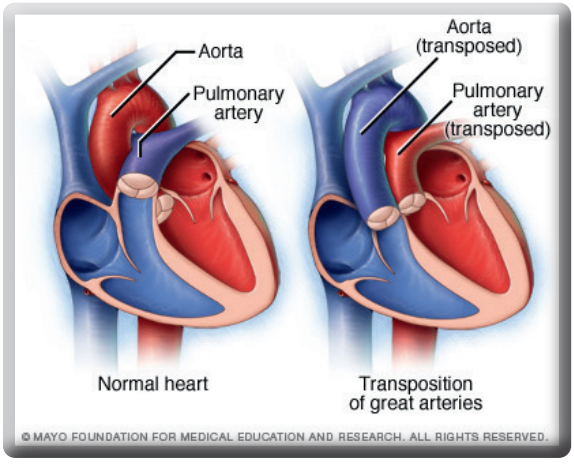
Congenital heart disease is the most common congenital abnormality, with an incidence approaching almost 1%. In infants born to diabetic mothers, the incidence is markedly increased, ranging between 3-6%. The reason behind this is unclear but it is postulated that exposure of the fetus to maternal hyperglycemia may cause the following: 1) altered gene expression affecting developmental pathways; 2) increased oxygen free radical formation leading to mitochondrial damage; 3) fetal hyperinsulinemia causing increased myocyte expression, leading to increased septal thickness.

The congenital heart diseases most commonly associated with infants of diabetic mothers may be classified as structural or functional. A structural defect denotes that there is something inherently wrong with cardiac formation. A functional defect implies that cardiac structure is inherently normal, however, the septal wall is just thicker than it should be. This septal thickness resolves in a few months, once the baby is no longer exposed to maternal hyperglycemia.

The most common structural congenital defects associated with infants of diabetic mothers are serious and complex. These defects include: 1) Transposition of the great arteries; 2) Tetralogy of Fallot; 3) Univentricular lesions such as Tricuspid Atresia and Hypoplastic Left Heart Syndrome; 4) Atrioventricular Septal Defect.

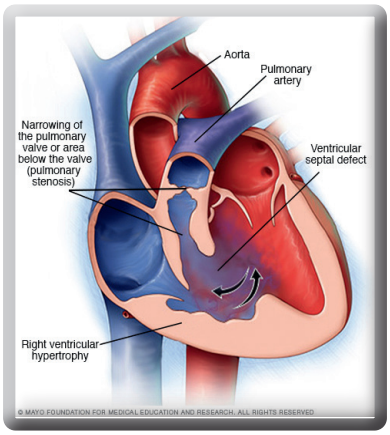
TRANSPOSITION OF THE GREAT ARTERIES

In transposition of the great arteries (TGA), the right ventricle gives rise to the aorta and the left ventricle gives rise to the pulmonary artery. Physiologically speaking, this creates two parallel circulations where deoxygenated blood is pumped back to the body and oxygenated blood is returned to the lungs. It is the most common congenital heart disease seen in infants of diabetic mothers. In the normal population, the prevalence of transposition of the great arteries is only 0.32%. In infants of diabetic mothers, the prevalence is estimated to range between 2-3.0%. Clinically, these patients are cyanotic. Surgery is needed, ideally done within the first few days of life.



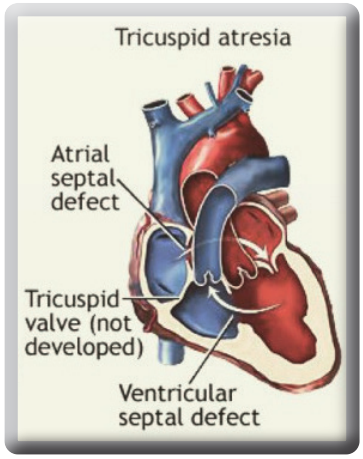
TETRALOGY OF FALLOT

Tetralogy of Fallot is another of the cyanotic congenital heart diseases. The four components are: infundibular stenosis across the pulmonary arteries; right ventricular hypertrophy; a large ventricular septal defect; and over-riding of the aorta. Because of the markedly decreased flow across the pulmonary arteries, patients are cyanotic. The degree of cyanosis depends on the severity of the infundibular stenosis. Like transposition of the great arteries, surgery will be needed. Because there is concomitant underdevelopment of the pulmonary arteries, further intervention will be required, even after surgery has been performed.



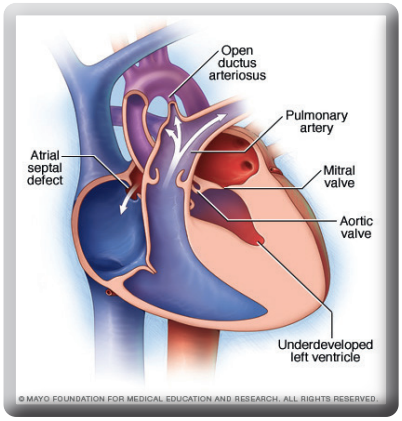
TRICUSPID ATRESIA

In tricuspid atresia, there is no functional tricuspid valve. Instead of a valve, there is a membrane preventing blood from exiting the right atrium. Because the blood is unable to leave the right atrium, the right ventricle receives less than the normal blood flow, causing the right ventricle to be underdeveloped and hypoplastic. Like transposition of the great arteries and Tetralogy of Fallot, patients present with cyanosis because blood flow to the lungs is compromised. Not only is surgery necessary, but a minimum of 2 operations is required in order to create a normal physiology.



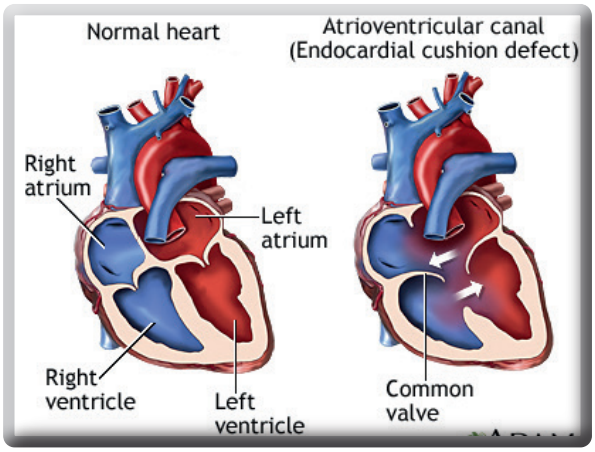
HYPOPLASTIC LEFT HEART SYNDROME

Hypoplastic left heart syndrome is a rare but very serious congenital heart disease. In hypoplastic left heart syndrome, there are multiple levels of obstruction across the left side of the heart. The mitral valve is severely stenotic. This then leads to decreased flow into the left ventricle, causing hypoplasia of the left ventricle. The aorta and ascending aorta receive less than the normal flow, and are thus, underdeveloped as well. These patients are extremely difficult to manage. Aside from the deficiency in systemic circulation providing flow to the body, these patients are cyanotic as well. The challenge is to balance blood flow between the systemic and pulmonary circulations. Multiple surgical procedures are needed to normalize flow with the first procedure necessary within the first few days of life.



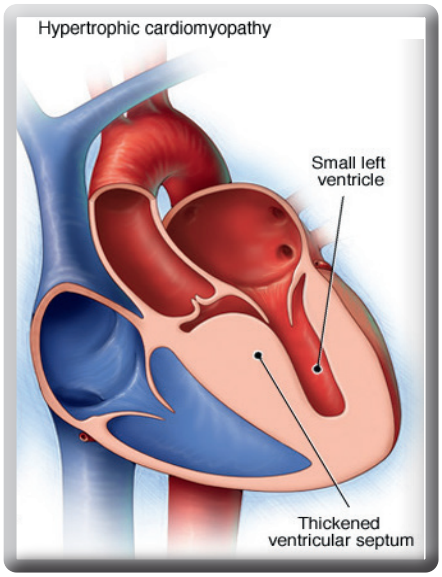
ATRIOVENTRICULAR SEPTAL DEFECT

As the name implies, there is a primum atrial septal defect, an inlet ventricular septal defect, as well as a common atrioventricular valve. Unlike the other lesions, these patients do not present with cyanosis. Because of the atrial and ventricular septal defects, more blood is coursed through the lungs. Congestive heart failure is the clinical presentation with dyspnea, tachypnea, and poor weight gain. Surgery is required, as with the other lesions identified above.



HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is the functional lesion seen in infants of diabetic mothers. The heart is structurally normal except for the interventricular septum, which becomes thicker. It is postulated that because of fetal hyperinsulinemia, there is increased myocyte expression manifesting as increased septal thickness. Majority of these patients are asymptomatic. If septal hypertrophy is severe, however, cardiac output will be compromised because of decreased blood flowing out into the aorta.



All of these lesions can be diagnosed early by a fetal echocardiogram. The echocardiogram is ideally performed between 18-24 weeks of gestational age. In identifying these fetuses early, both the family and the medical team have adequate time to prepare for the delivery of these babies.

The good news is that studies have clearly shown that good glycemic control can mitigate these adverse cardiovascular lesions on the fetus.

An international, multi-center study looked at Type 1 diabetic mothers and compared the incidence, types of congenital heart disease, and their HBA1c levels. The table on the left is data from the United States. The data in this study showed that Type 1 diabetic mothers with a higher HBA1c level had a higher incidence of babies born with congenital heart disease. The table on the right is data from the Netherlands and reflected similar findings.

The most common congenital malformations seen were transposition of the great arteries, heterotaxy and single ventricle physiology.

3 % of 557 infants	2.5% of 324 infants
HBA1c of those with affected infants=9.8 ± 0.7%	HBA1c of those with affected infants=7.4 ± 1.2%
HBA1c of those with unaffected infants=8.1 ± 0.3%	HBA1c of those with unaffected infants=6.5 ± 1.0%

Lisowski LA, et al. Herz. 2010 Jan; 35(1):19-26

Nashaat and his colleagues found that HBA1c levels also affect septal thickness. They looked at 100 diabetic mothers and divided them into controlled and uncontrolled groups based on their HBA1c levels. The cut off HBA1c value used was 6.3%. They then compared HBA1c levels and septal thickness in both groups and used 100 non-diabetic mothers as controls.

	CONTROLLED DIABETICS	UNCONTROLLED DIABETICS	NON DIABETIC
NUMBER	68	32	100
HBA1c	6.2 ± 0.72%	9.1 ± 1.6%	
SEPTAL THICKNESS	3.5 ± 1.24 mm (3 – 5 mm)	6.6 ± 0.878 mm (5 – 8 mm)	3.13 ± 0.68 mm (2 – 4 mm)

NashaatEH,etal.Researcher.2010;2(5)45-55

In a recent Centers for Disease Control and Prevention (CDC) study, researchers found that about 2670 babies in the United States could have been born without congenital heart disease. This included 75 babies born with hypoplastic left heart syndrome and 435 babies born with atrioventricular septal defect.

In summary, there is a higher incidence of congenital heart disease in infants of diabetic mothers. There is a structural and functional component to the cardiac lesions seen. The structural lesions are complex, often requiring open-heart surgery. These congenital heart defects can be detected by performing a fetal cardiac ultrasound, which helps in the preparation for the delivery of these babies. Most importantly, good glycemic control before and during pregnancy can mitigate the effects of hyperglycemia on the fetus.

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CV Outcomes of Prediabetes

Eugenio B. Reyes, MD, FPCP, FPCC

It has been observed that many patients who suffered a 1st cardiovascular event eventually become diabetic few months to a few years after the initial MI or stroke. Likewise, people who have been diagnosed with prediabetes (impaired fasting glucose and impaired glucose intolerance) who were optimally treated with risk-lowering interventions like statins, antiplatelet agents, ACE-inhibitors and other antihypertensive drugs and lifestyle modifications had a long event-free years of lives lived. These observations were validated in various epidemiologic studies which showed a strong association between prediabetes and cardiovascular events.[1] Studies have also shown that people with prediabetes have the same molecular and biological abnormalities as that of people with full-blown diabetes leading to the same macro- and microvascular outcomes.[2]

A systematic review of cohorts of people with impaired fasting glucose and impaired glucose tolerance showed a 20% higher risk of developing a stroke or MI.1 Prediabetes is therefore considered a precursor to cardiovascular disease but the impact may be modest. However, with the growing population, and with a prevalence of 7.2% in the Philippines[3], these translates to about 7.5 million Filipinos with prediabetes who are at risk to develop CVD. Both local and international guidelines have recommended testing people who are overweight or 45 years old and above with additional risk factors such as: physical inactivity, first-degree relative with diabetes, high-risk race/ethnicity, women who delivered a baby weighing >9 lbs or were diagnosed with GDM, hypertension (>140/90 mmHg or on therapy for hypertension), HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level 250 mg/dL (2.82 mmol/L), women with polycystic ovary syndrome, A1C >5.7%, IGT or IFG on previous testing, other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans), and a history of CVD.

But what can we do if we were able to identify them? It is important to note that prediabetes is associated with many modifiable risk factors like hypertension, low HDL, high triglycerides, and obesity.[4] Looking for these risk factors associated with atherosclerosis and treating them is therefore prudent in people with prediabetes. Treating hyperglycemia associated with prediabetes did not result in reduced CV mortality[5]. But treatment of hypertension and high cholesterol resulted in reduced CV death in patients with diabetes, prediabetes and even in patients with normoglycemia. Statins, so far, confer the greatest benefit. Exercise, diet, and weight loss showed a reversal of prediabetes to normal glucose tolerance. This is not an assurance, however, that the other risk factors will be controlled. It is important to determine whether lifestyle intervention impacts on these other factors.

The last thing that we need to understand about prediabetes aside from its glucose definition by numbers is: Is it a direct cause of CVD or is it just a marker? This has never been resolved. The data suggest that it may just be a predictor of CVD, a bystander. There are reasons to believe that it has no direct relationship with CVD. Treatment with glucose-lowering agents did not result in reduced CV risks. Although there are a few trials which showed benefits in lowering glucose, repeated clinical trials failed to demonstrate this.

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PH-LIPA-04-2014-09