مجلة العلوم الشاملة

Journal of Total Science

Higher Institute of Science & Technology

Raqdalen, Libya

البحوث المنشورة باللغات الأجنبية

Research Papers in Foreign Languages

Volume (2), Issue (7), (Sept. 2018)

Contents

Research Papers Published in Foreign Languages

Journal of Total Science
Volume (2), Issue (7), (Sept. 2018)
ISSN: 2518-5799

مجلة العلوم الشاملة
المجلد (2)، العدد (7)، (سبتمبر 2018)
ردمد: 2518-5799

Severe Hemolytic Anemia Due to Rh Incompatibility Case study

MR. ***Mohamed Khalifa Kanah. - Malak Suliman Jernaz. - Nora Issa Warragh. Dean of Medical Technology college – Department of Medical Laboratories, Medical Technology college, Nalut University***

فقر الدم الإنحلالي الحاد الناتج عن عدم توافق العامل الريزيسي(دراسة حالة)

ـ محمد خليفة قانة .2 ـ ملاك سليمان جرناز. 3- نورة عيسى ورغ.

Abstract

Background: Hemolytic disease of the Newborn (HDN) due to Rh incompatibility is characterized by the presence of anti D IgG antibodies in maternal circulation, which causes hemolysis in the fetus by crossing the placenta and sensitizing red blood cells RBCs leading to destruction of the RBCs by macrophages in the fetal spleen with resulting in hyperbilirubinemia, severe hemolytic anemia leading to severe anemia, jaundice, edema and usually abortion or delivering hydropsfetalis.

Aim: The present study was carried out to evaluate the prevalence of Hemolytic Disease of Newborn in Nalut hospital, Also to evaluate the efficiency in diagnostic and treatment approaches that take place in this case and whether human errors may play a major role in this situation.

Methods: Infants with HDN due to Rh incompatibility were taken as subjects and were compared with a control group of healthy infants. In addition, 40 mothers with Rh- negative were surveyed,

Conclusions: In our study, we concluded that alloimmune hemolytic anemia due to Rh incompatibility is the most common cause of HDN. On the other hand, HDN due to ABO was not detected in this study. The lack of administration of Anti D as a human error was the cause of this incident. blood group and antibody status, lack of maternal health education of the surveyed group.

Key Words: Hemolytic Disease of the newborn (HDN), Direct Antiglobulin Test, ABO Incompatibility, Rh Incompatibility

Object of the research – the reinforced concrete structures.

الملخص

أمراض إنحلال الدم للمواليد الناتجة عن إختلاف العامل الريزيسي ، تتميز بوجود مضاد للمستضد D من نوع IgG والمتواجدة في الجهاز الدوري للأم . وهذه المضادات تسبب انحلالا لدم الجنين عن طريق عبورها عبر المشيمة وإرتباطها وتفاعلها مع الخلايا الحمراء للجنين ، مسببتا تكسر وتدمير الخلايا الحمراء RBCs عن طريق الخلايا البيضاء الماكروفاج المتواجدة في طحال الجنين . وهذا يتسبب في زيادة نسبة المادة الصفراء hyperbilirubinemia ، إنيمية تحللية حادة تؤدي إلى فقر دم حاد ، يرقان ، وذمة وعادة اجهاض او ولادة اطفال في صورة غير طبيعية. تهدف هذه الدراسة لدراسة مدى انتشار مرض انحلال الدم للمواليد الناتج عن

الإختلاف في العامل الريزيسي في مستشفى نالوت ، وكذالك دراسة فعالية الطرق المستخدمة للتشخيص والعلاج لهذه الحالات ،
تم تجميع عدد من ا المواليد المصابين بإنحلال الدم الناتج عن اختلاف العامل الريزيسي وقورنوا بمواليد أصحاء .ايضا تمت دراسة 40 ام تحمل فصيلة سالبة وتم التركيز على دراسة حالة واحدة في هذه الدراسة .
النتائج : تم إستنتاج ان انحلال الدم للمواليد الناتج عن اختلاف العامل الريزيسي هو اكثر شيوعا من انواع انحلالات الدم للمواليد ،ولم نتمكن من الحصول على حالة من انحلال الدم ناتجة عن اختلاف فصيلة ABO في هذه الدراسة ، عدم إعطاء المصل المضاد للعامل الريزيسي Anti D كان السبب في حدوث هذه الحالة بالإضافة إلى عدم التعرف على فصيلة الأم او قياس الأجسام المضادة وضعف التوعية الصحية للأمهات .وقمنا بي تحليل أساليب الإنتاج لهيكل الخرسانة المسلحة ؛ بتسليط الضوء على أدوات هيكل الخرسانة المسلحة ، مثل : البلاطات الخرسانية .الاطارات ،الكمرات .الاعمدة. القواعد المشتركة .

Introduction:

Hemolytic disease of the newborn (HDN) due to Rh incompatibility has not been fully studied in Nafosa mountain. HDN most often is due to rhesus (Rh) incompatibility. While other types of blood group incompatibility such as ABO are less common. Most of Nalut population is Rh-positive. However Rh negative does not exceed 15% of the total population. Hemolytic disease of the newborn also known as erythroblastosis fetalis happens as a result of the positive immune response of the Rh-negative woman to Rh positive antigens whither from a previous blood transfusion or pregnancy or miscarriage or abortion.(Harmening;2012) Any situation that stimulates the response of the immune system by Rh positive antigen, without giving the recommended dose of Anti D also known as RhoGam. In this case the immune system of the mother will produce potent anti Rh especially to D antigen which the Rh negative mother is lacking, since these antibodies are both IgG and IgM; the big concern is antibodies of IgG that have low molecular weight and can cross the placenta to the fetus causing a severe hemolytic anemia leading to sever anemia, jaundice, edema and usually abortion or delivering hydropsfetalis.(Hu&Pen;2007)

Case Report:

On the Third of July 2014th, a newborn was delivered by a caesarian Section and was admitted to pediatric department at Nalut Central Hospital. The newborn wasn't crying, has difficulty and weak breathing, feverish, dehydration, and yellowish in appearance. After diagnostic investigation, it was known that the mother was Rh negative and the newborn was Rh positive and the mother has delivered the first baby 7 years ago and had four abortion after due the

sensitization of the mother as a result to failure of administration of anti D on time in the first place due to misidentification of the Rh negative.

Laboratory finding and blood work of the new born was as following: WBC:7.4_x10^3/dl, RBC:3.05_x10^6/dl, HB:11.9g/dl ,HCT:31.9% PLT: 290_x10^3/UL Differential WBC:LYM:57.6%, NEUT:33.8%. Blood sugar:78mg/dl. Blood group:O+ Rh positive . Total bilirubin was 15.9mg/dl, Direct bilirubin was 1.6mg/dl ALP IFCC Gen.2:289U/L Alanine Aminotrans .liquid:9U/L Aspartate Aminotrans.liquid:43U/L Na: 141.1mmol/L , K : 4.65mmol/L , CL : 110mmol/L Calcium Gen.2 : 7.0mg/dL ,Magnesium: 1.8mg/d.

Due to the limitation of therapeutic methods in Nalut hospital at that time, only phototherapy was administered to the patient, for 4 days starting on the 3ed of July tell 6th of July. The bilirubin levels and blood work worsens as indicated here:

Test /Date	3-7-2014	4-7-2014	5-7-2014	6-7-2014
Total Bilirubin	11.3mg/dl	15.9 mg/dl	22.1mg/dl	24.9mg/dl
Direct Bilirubin	0.6 mg/dl	1.6 mg/dl	2.5 mg/dl	3.4 mg/dl
HGB	11.9 g/dl	11.3 g/dl	10.4 g/dl	9.2 g/dl
RBC	3.05× 10^6/UL	3.00× 10^6/UL	2.85× 10^6/UL	2.61× 10^6/UL

Table (1) shows different results of T.B, D.B. HGB and RBC in 4 days respectively.

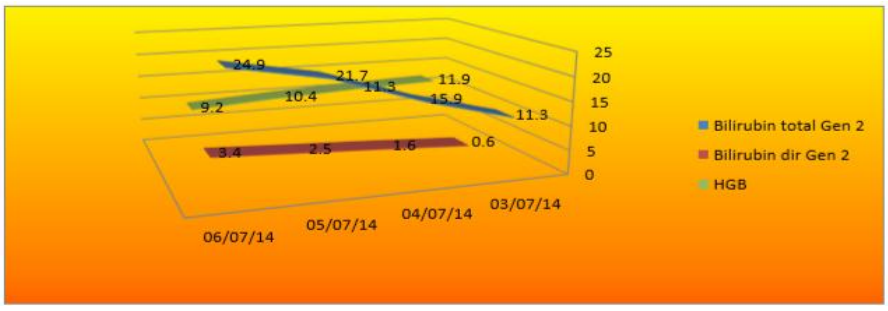


Chart shows test results of Hemoglobin, direct& total bilirubin of the case

Figure (2) Diagram shows the increase in total Bilirubin and direct Bilirubin while decrease in HGB in 4 days respectively.

Since it was not possible to do exchange blood transfusion due to some limitations in the pediatric Department and Blood bank in Nalut Central Hospital and to prevent further complications to the Newborn, Hence the patient was transferred to Tripoli Medical Center where he received exchange transfusion and was discharged later after improvement.

Desiccation:

HDN due to maternal-fetal blood incompatibility is a condition in which red blood cells in the fetus or neonate are destroyed by the action of antibodies.(Hu&Pen;2007) These antibodies are from the mother's immune system that was transported by a placenta. These antibodies are the IgG class which can cross the placenta because of the small molecular weight regardless of the rest of the antibodies produced by the immune system. The antibodies were formed against paternally inherited blood group antigens, usually the Rh (D) and A or B antigens.(Hu&Pen;2007) In this case, the antibodies are against Rh antigen, more precisely against the "D" gene that the mother lacks and the newborn inherited it from the father.

When HDN occurs, the lifespan of the red blood cells in the fetus or newborn is shortened dramatically (Contreras;2009). The hemolysis takes place starting from the intrauterine life of the fetus; destruction of fetal red cells degree or severity varies depending on the specificity, nature and concentration of the maternal antibody. Only a few of maternal red cell antibodies cause significant HDN such as anti-D, anti-K, and anti-c, may affect the fetus, especially when the antibody concentration is high. These antibodies can usually cause in most severe cases, fetal anemia and extravascular hemolysis which result in hepatosplenomegaly, ascites, subcutaneous edema, and pleural and pericardial effusions (hydrops fetalis). (Kumar; 2013)

Intrauterine death may occur in developed countries, as it is in this case for the previous pregnancies that pressed this case. In some cases where the severity of the disease is not that critical, the outcome might manifest as anemia as result of RBCs destruction, Jaundice which results from unconjugated hyperbilirubinemia accumulation since newborns liver is not mature enough to clear it from the system.

In this case, all the blood work indicates the severity of the disease and it is dramatically worsens during the four days of the patient admission. Which indicate the phototherapy alone, without exchange blood transfusion is not the best option for this case. As we can see for the Total Bilirubin test the results were: 11.3mg/dl, 15.9 mg/dl, 22.1mg/dl, and 24.9mg/dl respectively. The increase of Total Bilirubin indicates that the phototherapy is not effective in this situation to reduce the increase of bilirubin, which if not treated, will lead to impregnating the basal ganglia, causing spasticity and even kernicterus resulting in death or permanent cerebral damage, or mental disabilities. Hence the exchange transfusion should be considered. The limitation in neonate department does not allow the exchange blood transfusion to take place in Nalut Hospital, therefore; the patient was transferred to Tripoli Medical Center where the exchange transfusion was carried out and the newborn was discharged later upon improvement.

Different approaches and techniques were implemented for management and treatment of HDN due to Rh incompatibility, Double surface blue light phototherapy, exchange transfusion, and Intravenous immunoglobulin.

The Intravenous Immunoglobulin (IVIG) has shown promise for the treatment of HDN due to Rh incompatibility in terms of reduction of exchange transfusion, phototherapy and hospitalization days. While in HDN due to ABO incompatibility there was no significant difference between the methods listed above.(IVIG in Rh and ABO). (Nasseri; 2006)

However, a study conducted in the neonatal intensive care unit (NICU) at Gynecology and Obstetrics Hospital, Ain Shams University Egypt, over 28 months. The study included 116 neonates, with proven isoimmune hemolytic anemia due to Rh (n= 20) or ABO (n=96) incompatibility this study aimed to evaluate effectiveness of high dose Intravenous immune globulin (HD-IVIG) in reducing the need for exchange transfusion, duration of phototherapy and/or hospitalization in neonates with HDN due to Rh incompatibility or ABO incompatibility. The result of the study was that HD-IVIG effectively reduced the requirement for exchange transfusion and duration of phototherapy and hospitalization in isoimmune hemolytic disease of the newborn. (Habashy; 2014)

These methods are effective in terms of treatment with low risk and side effect of exchange transfusion which known to have an adverse reaction and increases the mortality and morbidity which may reach up to 74%, as a result increases the hospital stay and cost of treatment. (Abul& Andrew; 2011)

There is no significant difference between the gender of the newborn and the gravidity of the mother in terms of the effect of the outcome of the disease process.(Munker; 2007)

According to Nalut Central hospital records, there were about 198 delivery cases of Rh- negative women, of these deliveries, there wre about 160 newborns with Rh-positive, 23 cases of abortion were documented. On the other hand; 1915 delivery cases of Rh positive mothers were documented, of these deliveries, there was about 317 cases of abortion by the end of 2014.

We have surveyed 40 Rh-negative mothers and asked them several questions regarding their knowledge of the importance of Anti-D, how many children they had, and if there were any abortions or cases of HDN, also whether they were previously educated about their status regarding of being Rh negative mothers the results were:

28 cases of abortion since 2000-2014, 38 cases of anemia due to HDN,18 cases of acute hyperbilirubinemia most of them were treated by phototherapy, 4 cases had severe hyperbilirubinemia that required exchange blood transfusion. Unfortunately, we could not confirm this numbers and statistics of the surveyed mothers since a large number of medical files were not available. Hence the only confirmed case was reported in details in this paper, we will revise the paper further more if other cases were confirmed.

In general about 87% of the surveyed group stated that they had no knowledge or have been educated about their situation of being Rh negative and the importance and the outcomes of not taking the anti D in the first delivery.

Conclusion:

While treatment and prevention of hemolytic disease of a newborn have been improved recently and different approaches and medical procedures have been made (Bhutani; 2010) Still lack of maternal education and human laboratories errors may play a major role in the future cases of HDN. Hence more educational campaign and laboratories quality control techniques must be revised and updated, in

addition; adequate supply of Anti D to Central Hospitals and private and public clinics must be maintained and monitored. The access to RhoGam or Anti D must always be free of charge. Although anti D are being sold at private pharmacies, still the price may be a concern for low-income families, which puts the mother at great risk of developing anti D.

Furthermore, lack of laboratory quality control and not following the manufactures instruction plays a major rule in false results and human errors in medical laboratories. There is not enough data to measure the degree of laboratory errors since these are rarely documented. Unfortunately, there are some difficulties in determining medical responsibility; both in terms of medical errors from the laboratory technician & medical staff.

Therefore, the health sector or at least the Laboratory Medicine Association should establish committees to ensure the quality of medical laboratories and follow international standards and guidelines and enforce the laboratory stuff personal to adhere to these policies and guidelines.

Reference:

1-Hu, J. M., & Pen, H. S. (2007). Hemolytic Disease of the Newborn Due to Rh Incompatibility in a Neonatal Intensive Care Unit.Clinical Neonatology ,14(2), 46-49. Retrieved November 8, 2014.
2- Contreras, M. (2009). ABC of transfusion (2nd ed.). Hoboken, NJ: John Wiley & Sons Ltd.
3- Kumar, A. (December 2013). Hemolytic Disease of the Newborn: A study of 50 cases .International Journal of Scientific Study , 1(3), 95-99. Retrieved May 17, 2015.
4- Nasseri, F., Mamouri, G. A., & Babaei, H. (2006). Intravenous immunoglobulin in ABO and Rh hemolytic disease of newborn. Saudi Med J, 27(12), 1827-1830. Retrieved July 17, 2015.
5- Habashy, A. Safinaz .. etl . (2014). High dose intravenous immunoglobulin in Rh and ABO hemolytic disease of Egyptian neonates . Egypt J Pediatr Allergy Immunol, 12(1), 21-26. Retrieved April 27, 2015.
6-Abul K. Abbas & Andrew H. Lichtman. (2011). Basic immunology: functions and disorders of the immune system (3rd ed.). Philadelphia, , PA : Elsevier Inc.
7- Munker, R., Hiller, Glass, J., & Paquette, R. (2007). Modern hematology biology and clinical management (2nd ed.). Totowa, New Jersey: Humana Press In.
8- Bhutani- Vinod K, Zipursky- Alvin, Neonatal hyperbilirubinemia and Rhesus disease of thenewborn: incidence and impairment estimates for 2010 atregional and global levels, International Pediatric Research Foundation ,2013, Volume 74 , Number s1, 86-100
9-A. Elhabashy- Safinaz et al, High dose intravenous immunoglobulin in Rh and ABO hemolytic disease of Egyptian neonates, Egypt J Pediatric Allergy Immunology2014; 12(1):21-2
10-HARMENING. D. M (2012), Modern Blood Banking & Transfusion Practices (5th ed), by F. A. Davis Company .

Journal of Total Science
Volume (2), Issue (7), (Sept. 2018)
ISSN: 2518-5799

مجلة العلوم الشاملة
المجلد (2)، العدد (7)، (سبتمبر 2018)
ردمد: 2518-5799

Section of Civil Engineering and Construction

MR. AIMEN ABDULLAH ELSWAEE
Higher Institute of Science & Technology, Raqdalen, Libya

الهياكل الخرسانية المسلحة

طرق إنتاج هيكل الخرسانة المسلحة وأدوات البنية الخرسانية

الاستاذ ايمن عبدالله الصويعئ
المعهد العالي للعلوم والتقنية رقدالين

Abstract
The Reinforced concrete structures are one of the most popular structure systems. Reinforced concrete, as a unique symbiosis of concrete (sand, water, cement and special additives) and steel reinforcement connected in one simple or complex construct, is the most popular component in modern building.
The topicality of the study is analysis of the design methods of reinforced concrete structures.
The research aim is to analyze design methods of reinforced concrete structures and reinforced concrete structure tools.
The objectives of study:
To analyze the methods of production reinforced concrete structure;
To highlight reinforced concrete structure tools, such as:
Slab;
Beam;
Column;
Footing.
Object of the research – the reinforced concrete structures.

الملخص
الهياكل الخرسانية المسلحة هي واحدة من أنظمة البناء الأكثر شعبية. تعد الخرسانة المسلحة فريدة من نوعها للخرسانة (الرمل والماء والاسمنت والمضافات الخاصة) وتدعيم الفولاذ المتصل ببنية واحدة بسيطة أو معقدة ، هي المكون الأكثر شعبية في المبنى الحديث ،ويرتبط تاريخ الخرسانة بالبستاني الذي قام بين 1877 و1883 الذي قام بتصميم منتجات الخرسانة المسلحة . monje الفرنسي وتحدثنا في هذه الورقة البحثية عن

- طرق تصميم الهياكل الخرسانية المسلحة
- تحليل طرق تصميم الهياكل الخرسانية المسلحة وأدوات هيكل الخرسانة المسلحة

وقمنا بي تحليل أساليب الإنتاج لهيكل الخرسانة المسلحة ؛ بتسليط الضوء على أدوات هيكل الخرسانة المسلحة ، مثل : البلاطات الخرسانية .الاطارات ،الكمرات .الاعمدة. القواعد المشتركة .

Introduction

The Reinforced concrete structures are one of the most popular structure systems. Reinforced concrete, as a unique symbiosis of concrete (sand, water, cement and special additives) and steel reinforcement connected in one simple or complex construct, is the most popular component in modern building.

The topicality of the study is analysis of the design methods of reinforced concrete structures.

The research aim is to analyze design methods of reinforced concrete structures and reinforced concrete structure tools.

The objectives of study:

1. To analyze the methods of production reinforced concrete structure;
2. To highlight reinforced concrete structure tools, such as:

– Slab;
– Beam;
– Column;
– Footing.

Object of the research – *the* reinforced concrete structures.

T**he investigation subject – the** production methods of reinforced concrete structure and concrete structure tools.

The brief outline of the study structure: the study consists of introduction, two subparagraph, conclusion and bibliography.

1. METHODSOF PRODUCTIONREINFORCED CONCRETE STRUCTURE

Reinforced concrete products are made of concrete (cement, sand, water and fillers) and steel reinforcement. The history of the occurrence of reinforced concrete is associated with the name of the French gardener Monje, who between 1877 and 1883 patented railway sleepers, ceilings, beams, vaults and bridges of reinforced concrete [5, p. 12].

Since then, reinforced concrete has become one of the most popular materials used for construction. Its use in construction is justified by high rigidity, resistance to aggressive atmospheric influences, fire resistance, durability, ability to withstand high dynamic loads. The combination of concrete and reinforcement

reduces the cost of construction, improves the processability of the process.

There are monolithic reinforced concrete and reinforced concrete products. Monolithic reinforced concrete is used mainly in industrial and civil construction, and recently monolithic reinforced concrete and concrete products have often been combined, for example, in the construction of residential buildings, supporting structures are made of monolith, and enclosing and internal ones are made of lightweight concrete blocks.

Reinforced concrete products are much more versatile. They are used not only in mass construction, but also in private construction. Reinforced concrete is more durable than other modern building materials. Correct manufacture, installation and operation of reinforced concrete products extend the load-carrying capacity of concrete products practically for unlimited time, because with time, as the water evaporates, the concrete is strengthened, and the metal reinforcement inside the concrete is protected from corrosion [3, p. 110].

Before proceeding to the construction or manufacture of reinforced concrete products, it is necessary to carry out the appropriate calculations in order to determine the optimal composition of the concrete, the selection of the brand and the diameter of steel rods. Incorrect calculation can lead to the fact that the structures will be destroyed prematurely, and to overestimate the cost of construction.

Basics of production

In the production of reinforced concrete products, different methods are used to calculate their suitability for normal operation and load-bearing capacity of products. According to the nature of deformation loads, reinforced concrete products are divided into bent elements and centrally and eccentrically compressed elements. The first include slabs and beams, to the second – columns.

There are 2 forms of destruction and 3 stages of the stress-strain state of reinforced concrete.

Three stages:

- Before the occurrence of cracks in the stretched zone of concrete (reinforcement and concrete jointly take tensile forces);

- After the appearance of cracks (in the places of cracks forces are perceived by the armature, in the remaining zones – by reinforcement and concrete together);
- The stage of destructure (forces in the bending zone of the reinforcement reach the yield point of the material).

These three stages were the basis for experimental development of methods for calculating reinforced concrete products.

Forms of destruction

–On normal sections from the action of the moment of flection;

–On oblique sections from the use of inclined forces.

The calculation of the reinforcement is made when installed in tensile zone of concrete to prevent destructive deformations. Install the reinforcement in the direction of the intensity of tension, while the longitudinal reinforcement normalizes the stress on the concrete in normal sections, and the transverse – in inclined. In the compressed elements of the longitudinal reinforcement bars, it is equivalent to the concrete to perceive the load, and the transverse reinforcement protects the product from deformations with about a sixes [1, p. 230].

Methods for calculating reinforced concrete products

1. A method that involves calculating the corresponding cross sections for allowable stresses. In this method, a number of assumptions are adopted, the essence of which is reduced to the fact that the sectional area of the reinforcement is replaced by the sectional area of the concrete. In this case, concrete is considered as an elastic material, which does not allow to determine the actual stress in materials and to correctly calculate the safety factor of the product, leading to over-consumption of materials, in particular, reinforcement.

2. The method for calculating the destructive forces (by limiting states) is based on the establishment of limit states of the production with the introduction of a system of production coefficients that take into account the most unfavorable combinations of loads and the lowest strength indices of materials. This method allows saving a few resources in the manufacture of reinforced concrete products.

Values of forces corresponding to different types of exposure to the product, as well as resistance indicators of various steel grades for reinforcement. There are several types of forces:

- Constant – from the action of load-bearing and enclosing structures of buildings, the effect of soils;
- Permanent – from the impact of equipment permanently installed in the premises, force action in warehouses, temporary forces in residential buildings;
- Short-term– forces that affect on products and elements for a short time [4].

2. REINFORCED CONCRETE STRUCTURE TOOLS

2.1 Slab

The slab provides a horizontal surface and is usually supported by columns,
beams or walls. Slabs can be categorized into two main types: one-way slabs and
two-way slabs.
One-way slab is the most basic and common type of slab. One-way slabs are
supported by two opposite sides and bending occurs in one direction only. Two-way
slabs are supported on four sides and bending occurs in two directions. One-way
slabs are designed as rectangular beams placed side by side [2, p. 18]
However, slabs supported by four sides may be assumed as
one-way slab when the ratio of lengths to width of two perpendicular sides exceeds
Although while such slabs transfer their loading in four
directions, nearly all load is transferred in the short direction.
Two-way slabs carry the load to two directions, and the
bending moment in each direction is less than the bending moment of one-way slabs. Also two-way slabs
have less deflection than one-way slabs. Compared to one-way slabs, Calculation of
two-way slabs are more complex.
Types of Slabs
One-way slabs
1. One-way Beam and slab / One-way flat slab:

These slabs are supported on two opposite sides and all bending moment
and deflections are resisted in the short direction. A slab supported onfour sides with length to width ratio greater than two, should be designed as one-way slab.
2. One-way joist floor system:
This type of slab, also called ribbed slab, is supported by reinforced concrete ribs or joists. The ribs are usually tapered and uniformly spaced and supported on girders that rest on columns.
Two-way slab
1. Two-way beam and slab: If the slab is supported by beams on all four sides, the loads are transferred to all four beams, assuming rebar in both directions.
2. Two-way flat slab: A flat slab usually does not have beams or girders but is supported by drop panels or column capitals directly. All loads are transferred to the supporting column, with punching shear resisted by drop panels.
3. Two-way waffle slab: This type of slab consists of a floor slab with a length-to-width ratio less than 2, supported by waffles in two directions [2, p. 20].

2.2 Beam
Beams can be described as members that are mainly subjected to flexure and
it is essential to focus on the analysis of bending moment, shear, and deflection. When the bending moment acts on the beam, bending strain is produced. The resisting moment is developed by internal stresses. Under positive moment, compressive strains are produced in the top of beam and tensile strains in the bottom.
Concrete is a poor material for tensile strength and it is not suitable for flexure
member by itself. The tension side of the beam would fail before compression side
failure when beam is subjected a bending moment without the reinforcement. For
this reason, steel reinforcement is placed on the tension side. The steel reinforcement resists all tensile bending stress because tensile strength of concrete is zero when cracks develop [2, p. 24].

Fig. 2.1 shows the most common shapes of concrete beams: single reinforced rectangular beams, doubly reinforced rectangular beams, T-shape beams, spandrel beams, and joists.

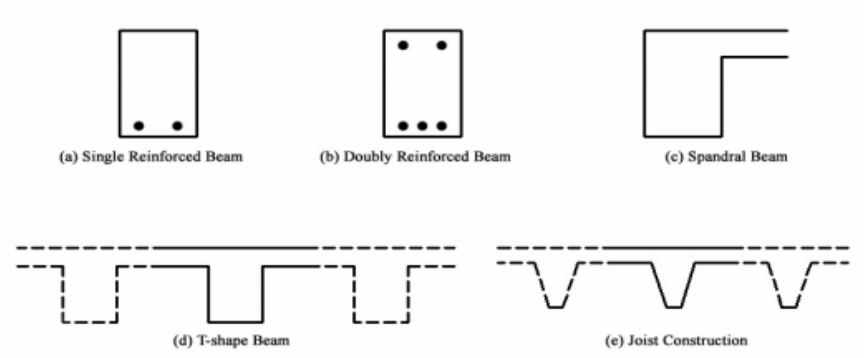


Fig. 2.1 –Common shapes of concrete beam

In cast–in-place construction, the single reinforced rectangular beam is uncommon. The T-shape and L-shape beams are typical types of beam because the beams are built monolithically with the slab. When slab and beams are poured together, the slab on the beam serves as the flange of a T-beam and the supporting 26 beam below slab is the stem or web. For positive applied bending moment, the bottom of section produces the tension and the slab acts as compression flange. But negative bending on a rectangular beam puts the stem in compression and the flange is ineffective in tension. Joists consist of spaced ribs and a top flange [2, p. 24].

2.3 Column

Columns support primarily axial load but usually also some bending moments. The combination of axial load and bending moment defines the characteristic of column and calculation method. A column subjected to large axial force and minor moment is design mainly for axial load and the moment has little effect. A column subjected to significant bending moment is designed for the combined effect. Compression force may cause lateral bursting because of the

low-tension stress resistance. To resist shear, ties or spirals are used as column reinforcement to confine vertical bars. The complexity and many variables make hand calculations tedious which makes the computer-aided design very useful.
Types of Columns. Reinforced concrete columns are categorized into five main types; rectangular tied column, rectangular spiral column, round tied column, round spiral column, and columns of other geometry (Hexagonal, L-shaped, T-Shaped, etc). The types of columns showed at the fig. 2.2 [2, p. 28].

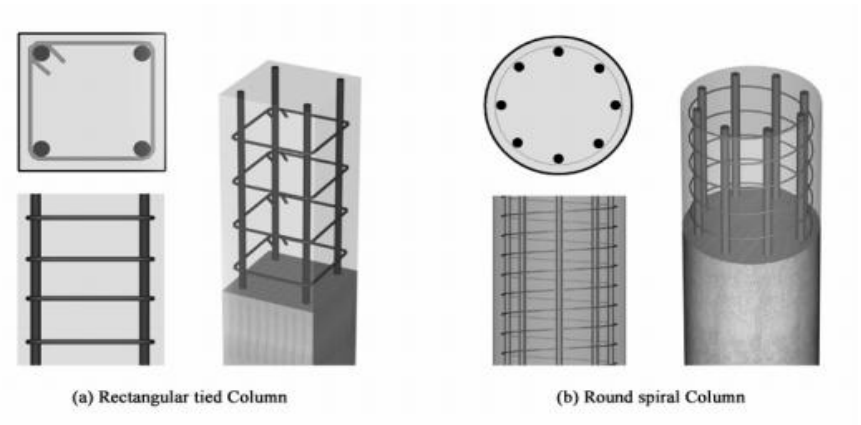


Fig. 2.2. – The types of columns

2.4 Footing

The foundation of a building is the part of a structure that transmits the load to ground to support the superstructure and it is usually the last element of a building to pass the load into soil, rock or piles. The primary purpose of the footing is to spread the loads into supporting materials so the footing has to be designed not to be exceeded the load capacity of the soil or foundation bed. The footing compresses the soil and causes settlement. The amount of settlement depends on many factors. Excessive and differential settlement can damage structural and nonstructural elements [2, p. 33].
Therefore, it is important to avoid or reduce differential settlement. To reduce differential settlement, it is necessary to transmit load of the structure uniformly. Usually footings support vertical loads that should be applied concentrically for avoid unequal

settlement. Also the depth of footings is an important factor to decide the capacity of footings. Footings must be deep enough to reach the required soil capacity.

Types of Footings

The most common types of footing are strip footings under walls and single footings under columns.

Common footings can be categorized as follow:

1. Individual column footing (Fig.2.3)

This footing is also called isolated or single footing. It can be square, rectangular or circular of uniform thickness, stepped, or sloped top. This is one of the most economical types of footing. The most common type of individual column footing is square of rectangular with uniform thickness.

2. Wall footing (Fig.2.3)

Wall footings support structural or nonstructural walls. This footing has limited width and a continuous length under the wall.

3. Combined footing (Fig.2.3)

They usually support two or three columns not in a row and may be either rectangular or trapezoidal in shape depending on column. If a strap joins two isolated footings, the footing is called a cantilever footing.

4. Mat foundation (Fig.2.3)

Mats are large continuous footings, usually placed under the entire building area to support all columns and walls. Mats are used when the soil-bearing capacity is low, column loads are heavy, single footings cannot be used, piles are not used, or differential settlement must be reduced through the entire footing system.

5. Pile footing (Fig.2.3) Pile footings are thick pads used to tie a group of piles together and to support and transmit column loads to the piles [2, p. 33].

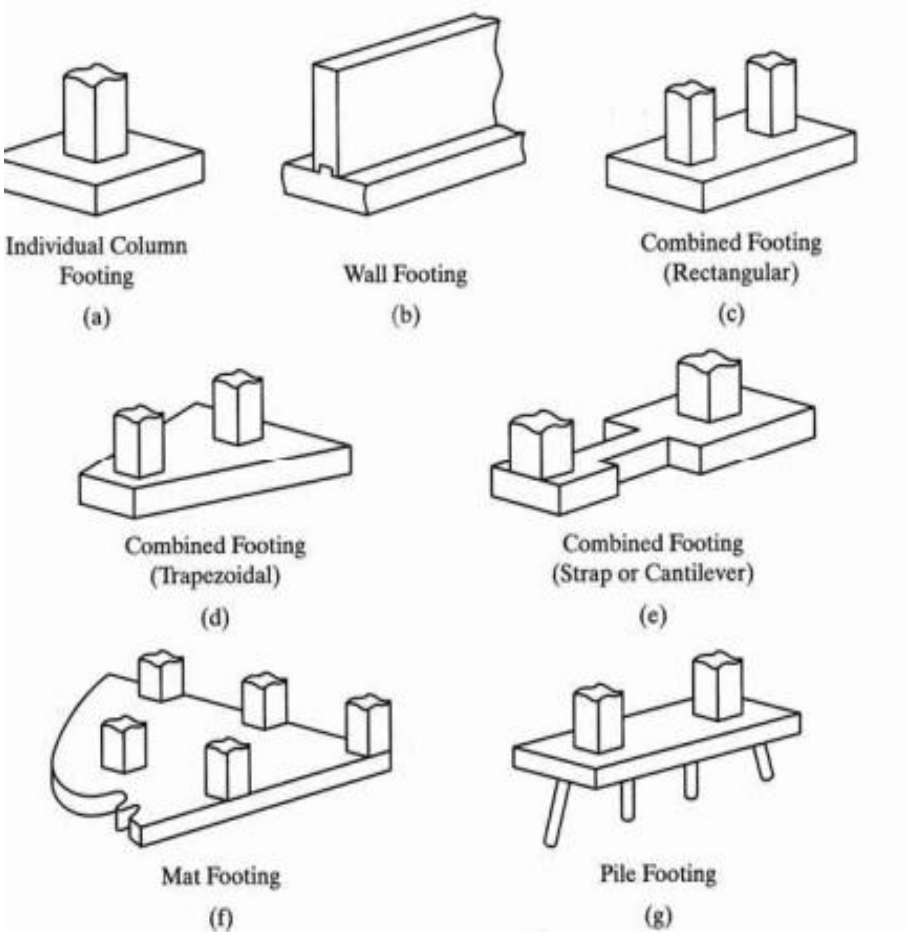


Fig. 2.3. – The types of footing

CONCLUSION

Reinforced concrete, as a unique symbiosis of concrete and steel reinforcement, connected in one simple or complex construct, is the most popular component in modern building. The history of the occurrence of reinforced concrete is associated with the name of the French gardener Monje, who between 1877 and 1883. In the design of reinforced concrete products, different methods are used to calculate their suitability for normal operation and load-bearing capacity of products.

There are 2 forms of destruction and 3 stages of the stress-strain state of reinforced concrete.

Three stages: before the occurrence of cracks in the stretched zone of concrete; after the appearance of cracks; the stage of destructure. These three stages were the basis for experimental development of methods for calculating reinforced concrete products.
Forms of destruction: on normal sections from the action of the moment of flection; on oblique sections from the use of inclined forces.
Reinforced concrete structure tools are:

- Slab – a horizontal surface and is usually supported by columns, beams or walls. Slabs can be categorized into two main types: one-way slabs andtwo-way slabs.
- Beams – members that are mainly subjected to flexure and it is essential to focus on the analysis of bending moment, shear, and deflection. The most common shapes of concrete beams: single reinforced rectangular beams, doubly reinforced rectangular beams, T-shape beams, spandrel beams, and joists.
- Columns. Reinforced concrete columns are categorized into five main types; rectangular tied column, rectangular spiral column, round tied column, round spiral column, and columns of other geometry.
- Footing – the foundation of a building.

BIBLIOGRAPHY

1. Ambrose, James E. Simplified Design of Concrete Structures, 7th ed.John Wiley & Sons, Inc., 1997.
2. Choi K. K. Reinforced concrete structure design assistant tool for beginners / K. K. Choi. – Faculty of the school of architecture university of southern California.– 153 p.
3. French, Samuel E. Reinforced concrete technology, Delmar Publishers, 1994.
4. Gamble, William L., and Park, Robert. Reinforced concrete slabs, John Wiley & Sons, Inc., 2000.
5. Hassoun, M. Nadim. Structural Concrete: theory and design, Addison-Wesley Publishing Company, Inc., 1998.
6. Nawy, Edward G. Reinforced concrete: a fundamental approach, Prentice Hall, 1996.
7. Nilson, Arthur H. Design of Concrete Structures, McGraw-Hill, Inc., 2000.

8. Parker, Harry, and Ambrose, James. Simplified Design of Reinforced Concrete, 5th ed., John Wiley & Sons, Inc., 1984.
9. Ray, S. S. Reinforced Concrete: analysis and design, Blackwell Science Ltd., 1994.
10. Williams, Alan. Design of Reinforced Concrete Structures, 2nd ed., Engineering press, 2000.

Journal of Total Science
Volume (2), Issue (7), (Sept. 2018)
ISSN: 2518-5799

مجلة العلوم الشاملة
المجلد (2)، العدد (7)، (سبتمبر 2018)
ردمد: 2518-5799

Glucose Derivatives for the Treatment of Type II Diabetes

Mrs. Wedad Ali Alagali Ahmed
Department of Biochemistry and Chemistry
Subratha University- Libya

مشتقات الجلوكوز لعلاج مرض السكري من النوع الثاني

الاستاذة/ وداد علي العجيلي احمد
كلية العلوم – قسم الكيمياء الحيوية
جامعة صبراتة

Abstract
Approximately 25.8 million people in the United States have diabetes. Diabetes is one of the leading causes of death and disability in the US. In type I diabetes, a person's immune system damages β-cells in the pancreas resulting in the inability to produce insulin. Impaired insulin secretion and insulin resistance occur in people with type II diabetes. More than 90% of affected individuals have type II diabetes. It is difficult to reduce all of the negative side effects that are caused by drugs. For this reason, it is important to continually synthesize new drugs in the hope of developing drugs with less adverse effects. The sodium–glucose co-transporters SGLT2 and SGLT1 are two isoforms of the SGLT family that are located in kidney, intestine, and brain. Both of these isoforms act to transport glucose in renal membranes to reabsorb glucose in the kidney. There are numerous studies investigating the inhibition of SGLT by glucose derivatives for the treatment of type II diabetes. Canagliflozin, Dapagliflozin, sergliflozin, and remogliflozen are glucose derivatives that decrease plasma glucose levels by inhibiting SGLT2 and SGLT1. The uptake of [^{14}C]α-methyl-D-glucopyranoside was studied in the absence and presence of various concentrations of the drug candidates in cells that expressed SGLT1 and SGLT2. From these studies, IC50 values were determined. The effects on the urine glucose excretion were studied by orally administration of the compounds into rats, collecting the urine, and determining glucose concentration using the glucose oxidase-peroxide detection method. These compounds were found to be inhibitors in both in vivo and in vitro. SGLT2 inhibitors are now in clinical trials for the treatment of diabetes.

Keywords: Type II Diabetes; Sodium–glucose Co-transporters SGLT2 and SGLT1; Canagliflozin ; Dapagliflozin; sergliflozin; and remogliflozen; [^{14}C]α-methyl-D-glucopyranoside.

الملخص

مايقرب من 25.8 مليون شخص في الولايات المتحدة الامريكية يعانون من مرض السكري. مرض السكري هو احد الاسباب الرئيسية للوفاة والعجز في امريكا. في النوع الاول من داء السكري، جهاز المناعة لدي الشخص يسبب ضرر لخلايا β في البنكرياس، مما يؤدي الي عدم القدرة علي انتاج الانسولين. اختلال افراز الانسولين ومقاومة الانسولين تحدث في الاشخاص الدين يعانون من مرض السكري من النوع الثاني. اكثر من 90 % من الافراد المتضررين مصابون بالسكري من النوع الثاني. من الصعب الحد من جميع الاثار الجانبية التي تسببها الادوية. لهدا السبب، من المهم ان يتم تصنيع ادوية جديدة باستمرار علي امل تطوير عقاقير ذات اقل تأثيرات ضارة. ان كلا من SGLT1 و SGLT2 هما من نوعين متشابهين من عائلة SGLT التي توجد في الكلي و الامعاء والدماغ. كل من هده الاشكال تعمل علي نقل الجلوكوز في الاغشية الكلوية لإعادة استيعاب الجلوكوز في الكلي. هناك العديد من الدراسات التي تبحث في تثبيط SGLT بواسطة مشتقات الجلوكوز لعلاج مرض السكري من النوع الثاني. Canagliflozin و Dapagliflozin و Sergliflozin و Remogliflozen هي مشتقات الجلوكوز التي تقلل مستويات الجلوكوز في البلازما عن طريق تثبيط SGLT1 و SGLT2 . تمت دراسة امتصاص α-methyl-D-glucopyranoside [14C] في غياب ووجود تراكيز مختلفة للأدوية في الخلايا التي عبرت عن SGLT1 و SGLT2 . من هده الدراسات، تم تحديد قيم IC50 و تمت دراسة التأثيرات علي افراز الجلوكوز في البول عن طريق تناول الادوية عن طريق الفم للجرذان، وتم تحديد الجلوكوز باستخدام طريقة كشف Glucose Oxidase- Peroxide Detection Method تم التأكد من ان هده المركبات هي مثبطات في كل من الجسم الحي وفي المختبر . مثبطات SGLT2 هي الان في التجارب السريرية لعلاج مرض السكري من النوع الثاني.

الكلمات المفتاحية- مرض السكر ي النوع الثاني II، ناقلات الصوديوم والجلوكوز
، Dapagliflozin، sergliflozin، emogliflozen، [^{14}C]α-methyl-D-glucopyranoside

Background

Diabetes is a familiar disease between different ages everywhere in the world. In the United States, it is estimated that about 25.8 million people from all ages have diabetes. Around18.8 million people have diagnosed with diabetes, and 7.0 million people have undiagnosed diabetes in 2011. [1] There are different kinds of diabetes, but the most common type of diabetes that affect about 90 to 95% of people with type 2 diabetes.[1] According to the National Diabetes Fact Sheet for 2011, 79 million of adults have prediabetes which is the major reason for people to have type II diabetes, and about 7 million do not know that they have prediabetes in the United States. On the other hand, in 2008, approximately 23.6 million of Americans had diabetes, and the number of adults with prediabetes was 57 million. According to Ann Albright, director of CDC's Division of Diabetes Translation, "We know that a structured lifestyle program that

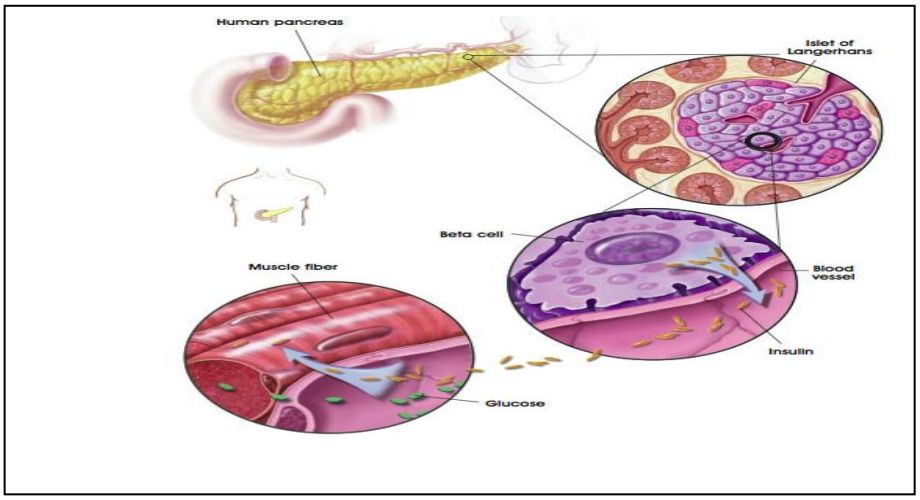
includes losing weight and increasing physical activity can prevent or delay type II diabetes."[2] Therefore, if the people do not do start living a healthy lifestyle, they will increase risk factors of type II diabetes, such as blindness, kidney failure, and obesity.[2] In the previous and currently studies, there are different treatments that target type II diabetes. For example, clinical studies have studied the different enzymes in the body of animals. These enzymes can be inhibited by derivatives of their natural substrate, such as glucose derivatives. In this paper, sodium–glucose co-transporters (SGLT2) was one of the enzymes that discussed. It is involved in the reabsorption of glucose in the kidney and can be inhibited by glucose derivatives.[3] SGLT2 is one isoforms of the SGLT family that is located in different places and it acts as transport glucose in intestinal and renal membranes.

Introduction

Food is a source of energy that is used by all organisms. One of the major sugars that have responsibility to increase high blood sugar is glucose. This glucose is accumulated in the blood when the pancreas does not produce enough insulin, or when the pancreas produces enough insulin, but the body cells such as liver, fat, and muscle cells cannot use the insulin for unknown reasons. This process is called insulin resistance and impaired insulin secretion, and it occurs in people with type II diabetes. Although the blood has enough glucose that provides energy in the body, glucose accumulates and causes high blood sugar which is called hyperglycemia.[1]

The pancreas is near the small intestine, and it has endocrine cells where the insulin is produced. Different types of endocrine cells are developed in the islets of Langerhans, which are beta cells, alpha cells, delta cells, and the PP-cells.The important part in these cells is beta cells because these cells produce the insulin that is important to people with both types of diabetes.[4] In the past, type II diabetes was called non-insulin -dependent diabetes mellitus (NIDDM).[1]

Figure 1: Some Component of Pancreas.[4]



This figure explains that: the pancreas is located in the abdomen near to small intestine. The islet of Langerhans that has important function in the pancreas is composed of β-cells. These cells response to produce the insulin when there is a decrease in glucose levels in the blood.[4] According to National Institutes of Health, when people are fasting, blood glucose should be at 100 (mg/dL) or lower, which means there is no diabetes. The risk for people with diabetes is if glucose levels are between 100 and 125 mg/dL during fasting time. When glucose levels are 126 mg/dL or more than this value during fasting time, people are diagnosed with diabetes.[5] In healthy people, β-cells located in the pancreas gland are responsible for producing insulin hormone that acts to transport glucose within body cells. Immune system acts as a protection system for β-cells in healthy people, but when this system fights and damages β-cells in the pancreas for unknown reasons, the insulin cannot be produced. Therefore people will have diabetes that is called type I diabetes. People with this type cannot live without taking insulin. Type II diabetes uses many kinds of oral inhibitors and insulin.4, in type I diabetes, children can have this type more than adult people. If this type of diabetes is not treated by taking insulin, the patients will go into a coma and could die. The symptoms of type I diabetes are felling thirst, fatigue, weight loss, blurred vision, and increase in urination. The type II diabetes occurs in adult people more than children, and it

is developed when a person has a family history, high blood pressure, obesity, high cholesterol, dark skin around the neck and armpits, or had diabetes while pregnant. [1] Some people do not have symptoms with type II diabetes, but some of them have these symptoms. For example, people may feel thirsty and blurred vision, and they may also have increase in appetite. Some of them have infections that are difficult and take long time to be healed. The fatigue and increase in urination are also symptoms for both types of diabetes mellitus.[6] Type II diabetes has different type of oral inhibitors, and it can treat with different drug programs. On the other hand, control of type 1 diabetes depends only on taking insulin every day. Both types of diabetes can be treated by using diet and insulin, but type 1 cannot be treated by using oral drug treatments. Therefore, this paper will discuss treatments for type 2 diabetes by using glucose depravities.[1]

Treatments

Diet is a program that helps people with diabetes to control blood glucose. Some people with diabetes can reduce their diabetes by following a diet from a dietitian. The dietitian explains to the patients how to know which food they should have. For example, a dietitian can give the patient a paper describing how many calories the patients need in the food and how many time to do exercise each day. Also, organization of meals by eating 4 or 5 times each day instead of eating one or two heavy meals can help because heavy meals have many calories that can increase glucose in the blood. Instead of eating a candy bar for a snack, the patient should eat an apple, and instead of eating rice with meet, the patient will be told to eat salad with meat.[7] When people follow the diet program, they will feel better. For example, when people with type II diabetes do exercises and eat healthy food with control of the calories, they will lose extra fat in their body, and they will organize their glucose levels in the blood. If the patients do not improved their type two diabetes, they should use different treatments such as insulin and oral therapy.[1] If the patents do not take care of themselves by doing the healthy programs such as diet or oral treatments, they will have health problems such as retinopathy, nephropathy, and neuropathy.[8] Also, if the patients do not take the treatments, their blood glucose will be high, and they will have chance to lose their lives by heart attacks, strokes, amputations, blindness, nerve damage, and kidney damage.[9] According to the National

Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in 1996, there was program called a diabetes Prevention Program. The goal from this program was to protect people from diabetes and to teach them how to decrease the risk of diabetes. It was an opportunity to people to delay or inhibited risk of getting type II diabetes. The program depended on diet and physical activity as long as the patient ate healthy food and walk at least 30 minutes each day. In 2001, the results were surprising because this program found approximately 58% of people had reduced the risk of getting type II diabetes, and it found that people lost about 5 -7% of body fat.[1]

Insulin: When patients do not find that their diabetes improved or that using a diet and exercise programs does not control their blood sugar levels, they should start to take oral medication. If there is still no regulation of diabetes, the doctors will advice the patients to take insulin.[6] Insulin is a drug that is taken by injection under skin. There are two kinds of insulin that help to control blood glucose during all day. Both of these kinds are given one or two times per day, and they reduce blood glucose all through the day. [9]

Table 1: Insulin That Lasts All Through the Day.[9]

Insulin That Lasts All Through the Day		
	Generic Name	**Brand Name**
	Intermediate-Acting Insulin	
Lasts All Day	NPH	Humulin N
	Novolin N	
	Long-Acting Insulin	
	Insulin detemir	Levemer
	Insulin glargine	Luntus

Intermediate-ActingInsulin: In this type of insulin, Neutral Protamine Hagedorn (NPH) is insulin crystals that should be made into a suspension solution by the pharmacy. NPH starts to work in the body after 2 or 4 hours from its taking. The efficient of this kind of the insulin can continue to 18 hours.[10]

Long-ActingInsulin: In this type of the insulin, insulin glargine and insulin detemir are two kinds of long acting insulin. They start to work in the body after 2 or 4 hours of injecting them. The efficient of these

kinds of the insulin can continue to 24 hours.[10] These kinds may not be enough for patients to control blood glucose. This means that some patients have hyperglycemia after eating the meal, and the insulin that is taken all through the day is not enough. Therefore, there are other types of insulin that are given at meal time. Fast-acting and short-acting insulin are act in short time, and they are taken two or more times each day.[9] **Table 2**: Insulin for Meal Times. [9]

Insulin for Meal Times	
Generic Name	**Brand Name**
Short-Acting Insulin	
Regular	Humulin R Novolin R
Fast-Acting Insulin	
Insulin aspart	Novolog
Insulin glulisine	Apidra
Insulin lispro	Humalog

Short-Acting Insulin: This type takes short time to work at about 30 minutes. Insulin is only one kind in short acting insulin, and the efficient of these kinds of the insulin can continue to 8 hours.[10] **Fast-Acting Insulin** In fast-acting insulin, Insulin glulisine, insulin lispro, and insulin aspart work fast at about 15 minutes of ejecting. It starts to work at the same time the patients start to eat. The efficient of these kinds of the insulin can continue to 3 and 4 hours. Since this kind of insulin leaves the blood stream fast, there will not be hypoglycemia.[10] There are some patients who need to use mixes of these types to make the injections of the insulin and the measurements to be easier. This table is for premixed insulin. "A 70/30 mix means 70 percent of the mix is longer lasting insulin and 30 percent is quick coverage for a meal.[9]

Table 3: Insulin That Covers Both All Day and Meal Times. [9]

Insulin That Covers Both All Day and Meal Times			
	Generic Name **NPH/ regular Insulin**	**Brand Name**	**premixed-**

Lasts All Day	NPH/regular 70/30 Novolin 70/30 Humulin 50/50	Humulin 70/30 NPH/regular 50/50
	Newer **Premixed** **Insulin**	
	Insulin aspart 70/30	Nonolog Mix 70/30
	Insulin lispro 75/25	Humalog Mix 75/25
	Insulin lispro 50/50	Humalog Mix 50/50

When compared between all of these kinds there were benefits in some of them. Compression between long-acting insulin and newer premixed insulin is in this table.

Table 4: Compared Between Long-acting Insulin and Newer Premixed Insulin.[9]

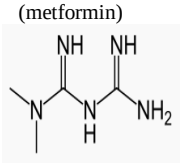
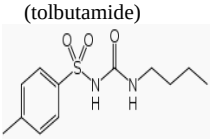
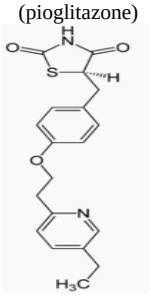
	Long-acting Insulin	**Newer Premixed Insulin**
Benefits		
Better at lowering A1c.		Yes
Better at lowering fasting Blood sugar (before eating)	Yes	
Better at lowering Blood sugar after meals.		Yes
Side effects		
Less hypoglycemia Very low blood sugar	Yes	
Less weight gain	Yes	

Medications of Therapy

This table shows some current drugs, their mechanism of action, positive effects and negative side-effects.[11]

Table 5: Some Current Treatments Choices for Patients with Type 2 Diabetes.

Pharmacologic Treat.Classes	Mechanism of Action	Effects/ Characteristics	Adverse Events

1. Biguanide (metformin) 	• Decrease hepaticglucose production • Decrease intestinal glucose absorption • Increase glucose uptake by skeletal muscle and fat	• Reduce blood glucose concentration • Increase sensitivity to insulin • Reduce blood lipid levels • Oral administration	• Diarrhea • Nausea • Vomitting • May cause lactic acidosis	
2. Sulfonylureas (tolbutamide) 	• Stimulate pancreatic ß-cell insulin secretion	• Reduce blood glucose concentration • Lower risk of hypoglycemia than insulin • Oral administration	• Hypoglyce-mia • Weight gain • Nausea • Vomiting	
3.Thiazolidinediones (pioglitazone) 	• Improve target cell response to insulin • Decrease hepatic glucose output • Increase insulin-dependent glucose uptake in skeletal • muscle and fat	• Reduce blood glucose conc. • Beneficial alteration of blood lipid levels • Possible beneficial effects on pancreas and cardiovascular risk factors • Oral administration	• Alteration in liver function indicators • Anemia • Detrimental cardiac effects Edema Weight gain	

Glucose Derivatives: There are many new inhibitors that can treat diabetes by decreasing plasma glucose levels (hyperglycemia), such as $SGLT_2$ inhibitors. This new class of glucose derivatives is discussed below.

SGLT2 Inhibitors

Sodium–glucose co-transporter 2 (SGLT2) is one member of the sodium-glucose co-transporters (SGLT) family of proteins, this family functions to transport glucose, amino acids, and vitamins cross

the membranes and cells of the body.[12] In healthy people, glucose is returned to the plasma instead of going to the urine by reabsorption presses in the kidney. These presses ensure the glucose can be reabsorbed by the body in the kidney instead of excreted in the urine. [3] This will be explained by the mechanism of action for SGLT2 below. It is important to know why glucose derivates do not inhibit SGLT1 instead of SGLT2. This is because SGLT1 is not the major glucose transporter in the kidney, but its major function is to transport glucose in the small intestine. Even SGLT1 transport glucose in the small intestine, it is not good to be inhibited in the small intestine. If the SGLT1 is inhibited by the drugs, the glucose can not pass through the intestinal wall. It stays and causes process called glucose-galactose malabsorption which is danger to patents lives because it causes "diarrhea and dehydration."[13] On the other hand, the results did not find any problems when SGLT2 was inhibited in the kidney.[8]

Mechanism of Action

In the kidney, increase amounts of renal glucose excretion by SGLT2 inhibitors, which act to inhibit SGLT2, decrease plasma glucose levels (hyperglycemia) and obesity in the body.[3] The location of SGLT2 is mainly in the S1 segment of the proximal tubule in the kidney.[3] SGLT1 is located in the intestines and in the S3 segment of the proximal tubule.[12] In a healthy people, when the plasma glucose is filtered in the kidney, about 99% of the plasma glucose is reabsorbed.[8] In the proximal convoluted tubule cells (PCT) that are in the kidney, 90% of SGLT2 and 10% of SGLT1 have responsible to reabsorbed the glucose. Glucose cannot across the membranes of lipids. Therefore, sodium in SGLT1 contacts with glucose to pass these membranes of lipids. ATP acts as protection to the sodium during transportation of sodium with glucose, and the glucose crosses the anti-luminal epithelium into the blood by another transports, glucose transporter type 2 (GLUT2) or glucose transporter type 1 (GLUT1), that help to transport the glucose.[3] Renal glucose reabsorption deals with the recovery of filtered glucose, and it prevents glucose from leaving the body to the urine. SGLT2 enzyme acts to transport the glucose from inside the kidney to out of the kidney. This presses called renal glucose reabsorption that is danger to the patients because glucose came from kidney to the plasma is filtered by filtrations that called glomeruli, and it goes to the blood

stream again. That is mean the blood will have increasing of the glucose. When the reabsorption possess occurs, the glucose cannot go into the urine. The glucose comes back into the body as occurs in the healthy people who need this glucose to keep their blood in balance. Therefore, if SGLT2 transporter that transports glucose is not inhibited, the patients will have hyperglycemia. In addition, glycosuria which glucose is excreted in the urine is important here because when SGLT2 is inhibited, the glucose stay inside the kidney and it goes to the urine. Subsequently, it will decrease plasma glucose levels.[3]

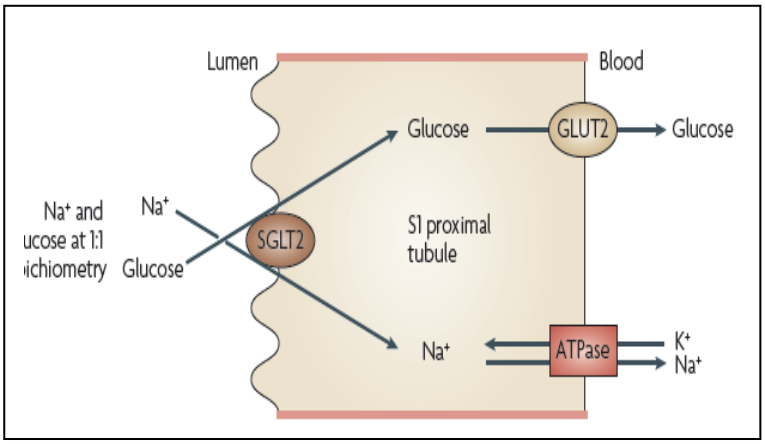


Figure 2: SGLT2 Mediates Glucose Reabsorption in the Kidney.[3]

Glucose Derivatives to Inhibit SGLT2 Enzyme:

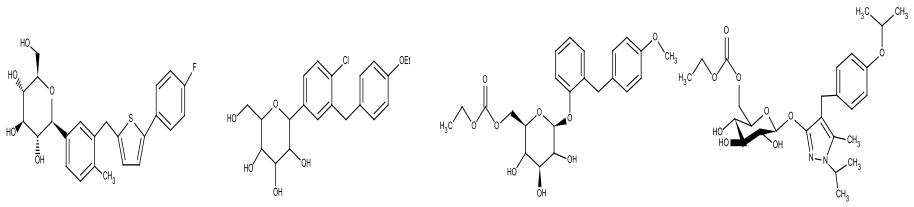
Classifications of SGLT2 Inhibitors

It is difficult to reduce all negative side effects that are caused by drugs so it is important to continually synthesize new drugs in the hope of developing drugs with less adverse effects.[3] There are two classes from glocoseside derivatives, which are O-glucoside inhibitors and C-glucosides are good inhibitors for people with type 2 diabetes. These drugs will be detailed below.

1. C-glycosides

C-glycosides are one class of glucose derivates. This class has a glucose attached to another group by a carbon-carbon bond. The carbon group in this class can be different kind of the other groups

which will be explained in the table 6. C-glucosides are more stable inhibitors than O-glucosides for sodium-dependent glucose co-transporter 2 (SGLT2). Canagliflozin, dapagliflozin, Sergliflozin, and Remogliflozin are examples for this class.[14]



Canagliflozin **dapagliflozin** **Sergliflozin**
Remogliflozin

Figure 3: Structure of Canagliflozin, dapagliflozin, Sergliflozin, and Remogliflozin.[14]

Canagliflozin: (4b-3) is a C-glucosides, and it prevents hyperglycemic. In a study, different groups were analyzed to find out which one of the groups is best to make the drug more effect on type 2 diabetes. Furan, thiophene, pyrazole, pyridine and thiazole were different gropes binded to C-glucosides producing new drugs. These drugs are different in their efficiency. These drugs were examined in this study by using mice that were 200 g in weight and that were fed a high-fat diet. When these mice were given these drugs the results during 24 h are discussed below.[14]

The Experiments
Measurement Urinary Glucose Excretion (UGE)[15]
The Method
1. Kasukabe rats (20-week-old) fed a high-fat diet (HF-KK) for 4 weeks. 2. Orally administer compounds or vehicle.
3.Collect urine samples for 24 hours.
4. Use Glucose Assay Kit to assay glucose concentrations in urine depending on using the glucose oxidase-peroxide reaction.

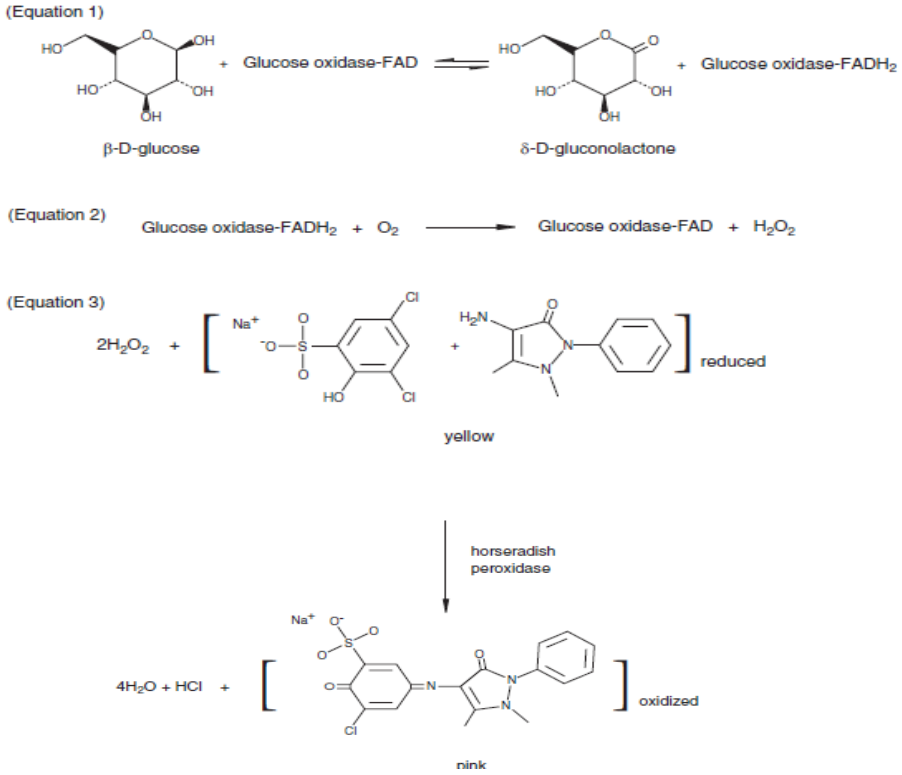


Figure 4: Glucose oxidase-peroxide reaction. [15]

5. Record absorption for both of patient and standard values at 514 nm.
6. Calculate the concentration of glucose.
   Abs. (Patient) / Abs. (Standard) x Concentration of Standard

(mg/dl) = Glucose (mg/dl)

7. Calculate UGE
Urine volume × Urine glucose concentration

Measurement Blood Glucose Level[16]

1. Collect blood samples from tail vein before taking the drug and after at 1, 2, 4, 6 and 24 hr.
2. Measure blood glucose level using commercially available kits

$$\int_a^b f(x)\,dx = \Delta x / 2\,(y_0 + 2y_1 + 2y_2 + \ldots.. + 2y_{n-1} + y_n)$$

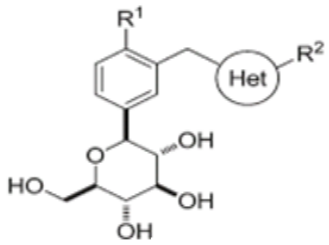
Where $\Delta x = b - a / n$

Determination of IC_{50}. [17]

1. Plate cells expressing SGLT1 and SGLT2
2. Rinse and incubate with solutions of compounds for 10 min
3. Initiate transport reaction with alpha ^{14}C-methyl-D glucopyranoside (AMG) and incubate for 120 min
4. Stop ^{14}C-AMG uptake by washing the cells
5. Solubilize the cells and count radioactivity by a liquid scintillation counter
6. Determine 100% of transport from sample without inhibitors
7. Repeat with various concentrations of inhibitors

The Results and discussion

The table shows that IC50 values for SGLT2 activity and urinary glucose excretion (UGE) are different between these derivatives. The better compound, 4b-3 (Canagliflozin), was chosen as a clinical applicant because it has high SGLT2 inhibitory activity, and it also has high (UGE) urinary glucose excretion effect. The other compounds have less SGLT2 inhibitory activity and (UGE) effect respectively.[14]



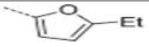
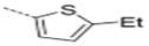
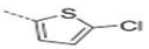
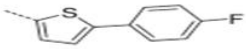
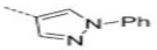
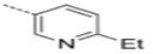
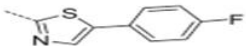
compd	R^1	Het-R^2	hSGLT2 IC_{50} (nM)	UGE[a] (mg/day)
4a-1	H		920	N.D.[b]
4b-1	H		17	373
4b-2	Cl		2.4	2495
4b-3	Me		2.2	3696
4c-1	Cl		32	N.D.[b]
4d-1	Cl		28	N.D.[b]
4e-1	Me		8.1	1277

Table 6: *C*-Glucosides with Heteroaromatic Ring.[14]

In figure below, when 3 mg/kg of compound 4b-3 was given to these mice, reduction in blood glucose level were observed after 6 h when these results were compared with the vehicle, which mean there are not any medicine were given to these mice, there was only 48% of this reduction.[14] These results also showed that urinary glucose excretion was increased when these rats were administered 4b-3. This mean, when the urinary glucose excretion increases, the glucose will be reduced in the body. This is good news for this kind of drug because it helps people with type II diabetes to control their problem.[14]

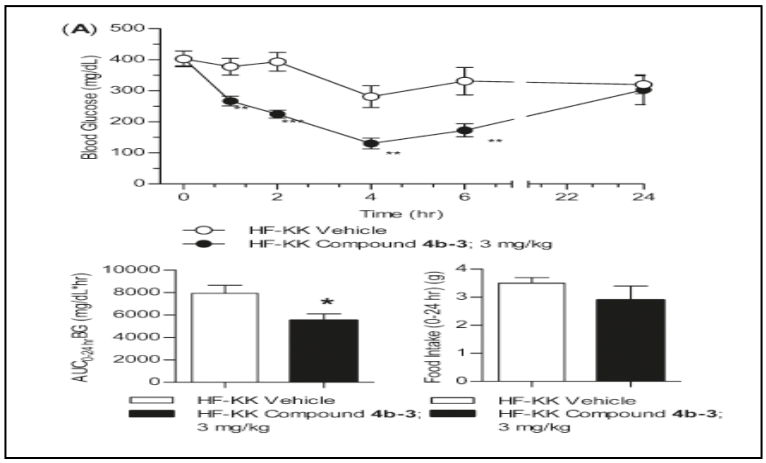


Figure 5: Effects of Single Oral Dosing of 4b-3 on Blood Glucose Levels and Food Intake in High-fat Diet Fed KK (HF-KK) (A) and Normal.[14]

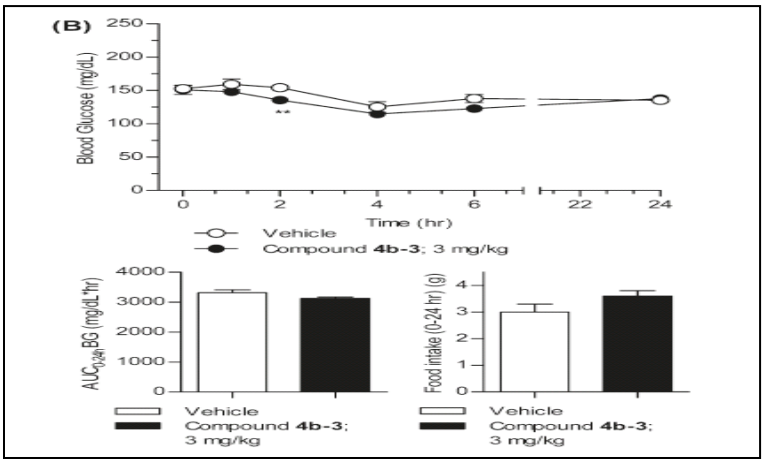


Figure 6: Effects of Single Oral Dosing of 4b-3 on Blood Glucose Levels and Food Intake in Normal (B) Mice.[14]

Dapagliflozin

Dapagliflozin is a selective hSGLT2 inhibitor class of C-arylglycoside in phase III clinical trials.[8] Dapagliflozin has been shown to decreases hyperglycemia in blood by using streptozotocin rats (STZ) that have hyperglycemia.[13]

In the experiment of Meng and his group, streptozotocin (STZ) rats which have diabetes were given oral dose of dapagliflozin at 0.1 mg/kg. After 5 h of eating the food and the oral does, blood glucose levels had decreased by 55%. Their blood glucose levels were more than 500 mg/dl before the rats took dapagliflozin. Also, they could obtain the same results when 0.01 and 0.03 mg/kg of oral dose of dapagliflozin were given to the rats after 5 h. The results were 17% and 45% reduction of blood glucose levels respectively. Therefore, based of these results, we can expect that dapagliflozin, may be good treatment for type II diabetes. It shows that blood glucose is reduced compared to the vehicle. [13]

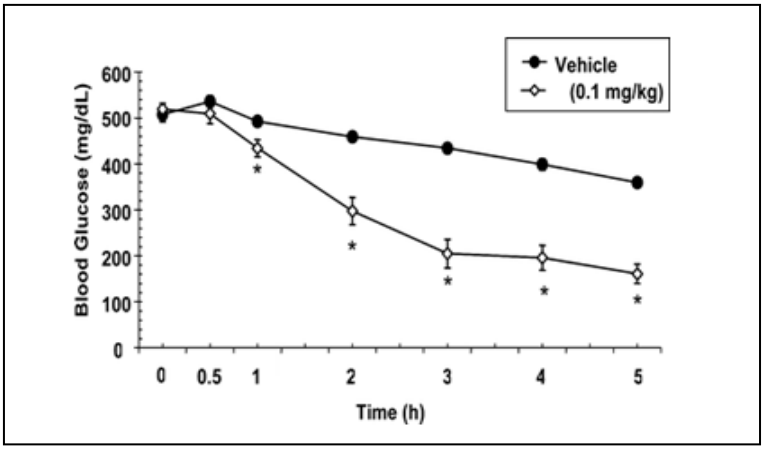


Figure 7: "Mean blood glucose values in STZ-induced diabetic Sprague –Dawley rats following a single oral dose of 0.1 mg/kg" [13]

2. O-glycoside

O-glycosides are class of glucose derivates. This class has a group attached to the glucose by a glycosidic (C-O) linkage.

Sergliflozin and Remogliflozin

In 2003, Kissei suggested the use of Sergliflozin to treat diabetes and obesity, and he later developed remogliflozin. These drugs are inhibitors for type II diabetes. Sergliflozin and remogliflozin are inhibitors of SGLT2 with high selectivity.[3] Researchers compared oral dose of sergliflozin with placebo for 14 days. The results were

suppression of renal glucose reabsorption. Also, the body weight was decreased at 0.09 kg in the placebo by using 1000 mg of the drug. Also, 1.55 and 1.74 kg were decreased from the body weight when 500 mg and 1000 mg was used from sergliflozin . Oral dose of remogliflozin was used to increase urinary glucose excretion. These drugs also reduced plasma glucose levels and glycated haemoglobin, their side effects were the reason to stop use them.[3] In the gastrointestinal, both of these drugs have O-glucoside linkages that cause in their hydrolysis by enzymes such as β -glucosidase.[3]

Conclusion

Glucose derivatives targeting SGLT1 and SGLT2 have the potential to provide a new treatment for type II diabetes. These compounds were found to be inhibitors in both in vivo and in vitro. SGLT2 inhibitors are now in clinical trials for the treatment of diabetes. Finally, even though clinical trials improve different kinds of inhibitors; there are some drugs that are not effective and are stopped for different reasons.

Acknowledgements

The author would like to acknowledge Professor Elizabeth S. Roberts-Kirchhoff, and Professor David Bartely for their guidance and their suggestions. The author thanks the University of Detroit Mercy and the Department of Chemistry and Biochemistry for their considerations.

References

1. ***National Diabetes Information Clearinghouse: Service of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health***.
http://diabetes.niddk.nih.gov/dm/pubs/overview/
2. ***Centers for Disease Control and Prevention.***
http://www.cdc.gov/media/releases/2011/p0126_diabetes.html
3. Chao, E. C.; Henry, R. R. ***SGLT2 Inhibition — A Novel Strategy for Diabetes Treatment. Nature***. Reviews | Drug Discovery. Vol. (9), No. (7), pp. 551-558, (**2010)**.
4. ***The National Institutes of Health Resource for Stem Cell Research.***
http://stemcells.nih.gov/info/scireport/chapter7.asp#Bosco

5. ***U.S. National Library of Medicine. Department of Health and Huma Services National Institutes of Health.***
http://www.nlm.nih.gov/medlineplus/ency/article/003482.htm
6. ***U.S. National Library of Medicine. Department of Health and Human Services National Institutes of Health.***
http://www.nlm.nih.gov/medlineplus/ency/article/000313.htm
7. ***The Federal Citizen Information Center of the U.S. General Services Administration.***
http://www.pueblo.gsa.gov/cic_text/health/noninsulin-diabetes/diet.htm
8. Goodwin, N.C.; Mabon, R.; Harrison, B. A.; Shadoan, M. K.; Almstead, Z. Y.; Xie, Y.; Healy, J.; Buhring, L.M.; DaCosta, C. M.; Bardenhagen, J.; Mseeh, F.; Qingyun, L.; Nouraldeen, A.;Wilson, A. G. E.; Kimball, S. D.; Powell, D. R.; Rawlins, D. B. ***Novel L-Xylose Derivatives as Selective Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitors for the Treatment of Type 2 Diabetes.*** *J. Med. Chem.* Vol. (*52*), No. (20), pp. 6201–6204, (2009).
9. ***Premixed Insulin for Type 2 Diabetes.*** AHRQ. Vol. (*8*), No. (9), pp. 1-13, (2009).
10. ***American Diabetes Association***
http://forecast.diabetes.org/magazine/resource-guide/insulin-and-other injected-drugs
11. Hinnen, D.; L. NielseN, L.; Waninger, A.; Kushner, P. ***Incretin Mimetics and DPP-IV Inhibitors: New Paradigms for the Treatment of Type 2 Diabetes.*** JABFM. Vol. (*19*), No. (6), pp. 612-620, (2006).
12. Yao, C-H.; Song, J-S.; Chen, C-T.; Yeh, T-K.; Hung, M-S.; Chang, C-C.; Liu, Y-W.; Yuan, M- C.; Hsieh, C-J.; Huang, C-Y.; Wang, M- H.; Chiu, C-H.; Hsieh, T-C.; Wu, S-H.; Hsiao, W-C.; Chu, K-F.; Tsai, C-H.; Chao, Y-S.; Lee, J-C. ***Discovery of Novel N-β-D-Xylosylindole Derivatives as Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitors for the Management of Hyperglycemia in Diabetes.*** *J.* Med. Chem. Vol. (*54*), No. (1), pp.166–178, (2011).
13. Meng, W.; Ellsworth, B. A.; Nirschl, A. A.; McCann, P. J.; Patel, M.; Girotra, R.N.; Wu, G.; Sher, P.M.; Morrison, E. P.; Bille, S. A.; Zahler, R.; Deshpande, P.P.; Pullockaran, A.; Hagan, D.L.; Morgan, N.; Taylor, J. R.; Obermeier, M.T.; Humphreys, W. G.; Khanna, A.; Discenza, L.; Robertson, J. G.; Wang, A.; Han, S.; Wetterau, J. R.; Janovitz, E. B.; Flint, O. P.; Whaley, J. M.;

Washburn, W. N. ***Discovery of Dapagliflozin: A Potent,*** *Selective* ***Renal Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitor for the Treatment of Type 2 Diabetes.*** J. Med. Chem Vol. (*51*), No. (5), pp. 1145–1149, (2008).

14. Nomura, S.; Sakamaki, S.; Hongu, M.; Kawanishi, E.; Koga, Y.; Sakamoto, T.; Yamamoto, Y.; Ueta, K.; Kimata, H.; Nakayama, K.; Tsuda-Tsukimoto, M. ***Discovery of Canagliflozin, a Novel C-Glucoside with Thiophene Ring, as Sodium-Dependent Glucose Cotransporter 2 Inhibitor for the Treatment of Type 2 Diabetes Mellitus.*** J. Med. Chem. Vol. (*53*), No. (17), pp. 6355–6360, (2010).
15. ***Cayman Chemical Company*****.** **http://www.caymanchem.com/pdfs/10009582.pdf**
16. **http://www.solitaryroad.com/c376.html**
17. ***National Institutes of Health Chemical Genomics Center.*** **http://assay.nih.gov/assay/index.php/Section5:Binding_Parameters**