Microalbuminuria & Glycosilated Hemoglobin

Two key parameters to prevent late diabetic complicatons

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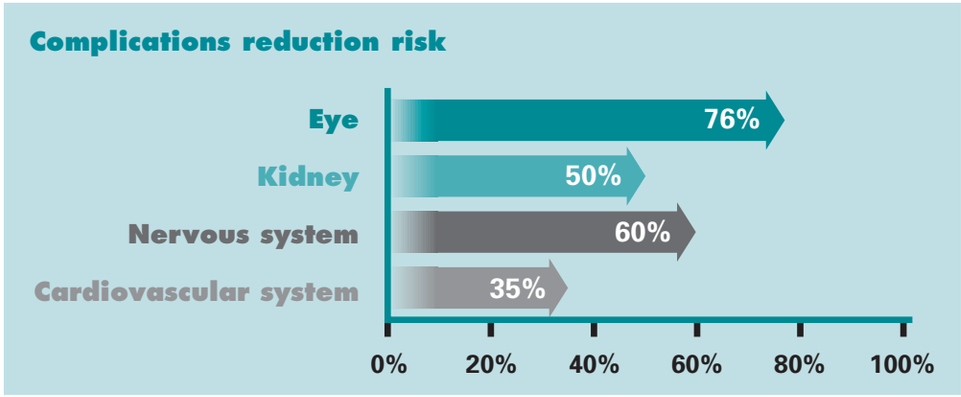
Introduction

Diabetic complications reduction risk

As the DCCT study has definetively prooven in 1993 the incidence and the severity of the diabetic complications can be dramatically reduce when the degree of diabetic control is improved.



During the 10 years follow up of the DCCT study thare was a 39% reduction of the development of microalbuminuria in the intensive treated patients.

The Glycosilated Hemoglobin shows the ponderated average of the glycemia during the previous three months.

The Microalbuminuria: is an early marker of kidney disease and detect an increased cardiovascular risk. It has been clearly demostrated that treating it timely and correctly can improve the outcome.

All that reasons has made that worlwide the main Diabetic Associations has recommended to perform it at least yearly.

Importance of the diabetic nephropathy

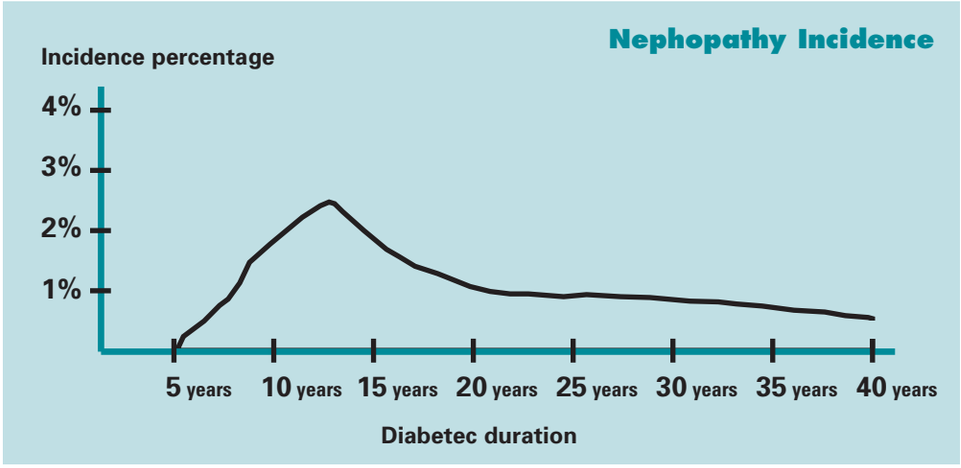
Up to 25% of all the patients diagnosed of renal failure and 33 % of all the patients who requires dyalisis or renal transplant are secundary to diabetic nephropathy.

Diabetic Nephropathy is the first cause of dyalisis in the developed world.

Between 30-40% of type 1 diabetic patients are expected to develop diabetic nephopathy while this porcentage is reduced to 10-20% in type 2 diabetic patients. Obviously because the different numbers the mayority of renal failure secondary to diabetic nephopathy are in type 2 diabetic patients.

How diabetic nephropathy is diagnosed?

The damage to the kidneys start very early, well before the microalbuminuria turns positive this is the "silent phase" of the diabetic nephropathy during that phase is possible to demostrate typical diabetic changes as mesangial expansion and thickening of the basal membrane.



Epedimological data shows that in type 1 diabetic patients the diabetic nephopathy start after 10-15 years of diabetic duration (Scheme taken from Krolewski).

In the type 2 diabetes patients is possible to demostrated the presence of microalbuminuria at diagnoses in 13% of them; and macroproteinuria in 6 % of the cases.

In summary in type 2 diabetic patients, diabetic nephopathy is less frequent but often the diagnostic is made in the first 10 years after the clinic diabetes diagnoses although who know that the hyperglycemia has been present for years before.

The fact that the diabetic nephopathy may occur without symptoms makes mandatory to screen periodically for microalbuminuria in all the diabetic patients because it will be not found in the routine urine analysis.

The abnormal blood test are more delayed because the rise in the creatinine values does not start untill there is a loss of 40-50 % of the working nephrons.

The best treatment will start before the microalbuminuria turns positive but we need to develop earlier markers what may allow us in the future to change the natural history of the diabetic nephopathy.

What is microalbuminuria?

Microalbuminuria is the loss in the urine of abnormal high amounts of albumine. (Check the following table):

Proteinuria diagnostic criteria in Diabetes Mellitus

	24 h urine	Albumine/creatinine index	Timed urine
Normal	< 30 mg/24 h	< 30 mg/g	< 20 ug/min
Microalbuminuria	30-300 mg/24 h	30-300 mg/g	20-200 ug/min
Proteinuria	> 300 mg/24 h	> 300 mg/g	> 200 ug/min

Microalbuminuria is a well known diabetic nephopathy marker since the early 80´s.

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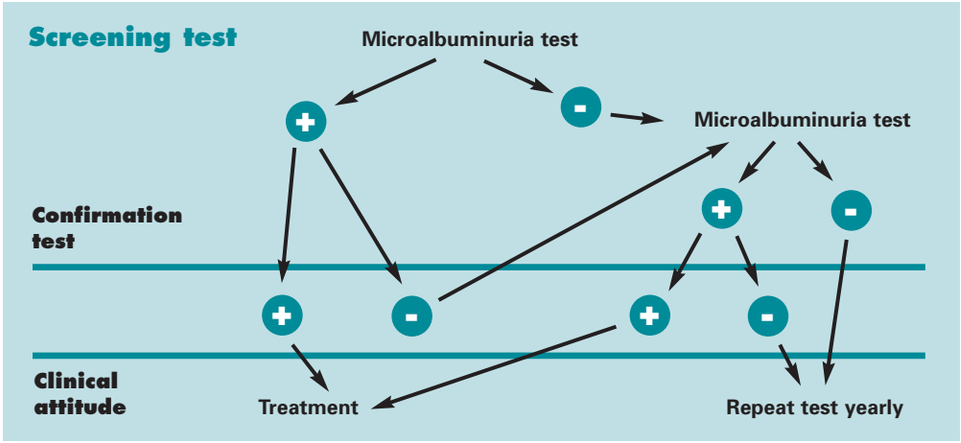
How diabetic nephropathy is diagnosed?

Regardless of the diabetes type the determination of microalbuminuria is mandatory yearly in all the diabetic patients older than 12 years old.

A panel of experts in the American Diabetes Association has designed an algorism for the screening and the microalbuminuria diagnostic criteria:



ADA Microalbuminuria screening and confirmation algorism.

There is a consensus that the screening can be made easily by the albumine/creatinine ratio in any urine sample to date there is not enough longterm studies that demostrate which is the best collection method but the first morning urine is generally prefered because the concentration in the urine is higher and that allows a better albumine determination when an abnormal result is found in the screening test is recommended to perform a cuantitative test with the nightime urine collection or 24 hours urine collection.

It is important to remind that the nightime albumine excretion is a 30-50% lower than during the day.

In order to establish a diagnoses of persistent microalbuminuria is necessary at least two positive results in three consecutive urine test made in an 3 or 6 months interval. All this precations are necessary because there is a big biologic variability around 40% precautions.

Factors that may modify the microalbuminuria results

There are some factors that can create confusion when testing microalbuminuria values, we represent then in the following table in next page:

Microalbuminuria modifyng factors

- Biologic variability
- Exercise
- Urine infection
- Cardiac failure
- Urologic, tumors and stones
- Severe hyperglycemic episodes
- Acute illness
- Drugs, gentamicine, NSAA
- Menses

Different methods for microalbuminuria determination

There are several microalbuminuria determination methods, Immunoassay, Nephelometric, etc...

All this methods are easily automated allowing the determination of a big number of samples in a short period of time but it is expensive and not available in many centers.

In contrast microalbuminuria reagent strips and pills are cheap and quick methods but they are just semiquantitative test and may lead to errors due mainly for changes in the urine concentration. All this make necessary to confirm by other more specific methods all the positive results. When the microalbuminuria results are given in correlation with the creatinine urine excretion all the problems created by the different urine concentration are solved.

The DCA 2000 is a quick automatic turbidometric method.

Microalbuminuria in the general population

Between 5-10 % of the healthy population has positive microalbuminuria. When we select a population like those subjects with hypertension then the percentage can be as high as 20-40 %.

Although it has been clearly demostrated that the microalbuminuria existance is a mortality cardiovascular risk factors it cannot be concluded if it is by the microalbuminuria itself or because is associated to other well knows risk factors as hypertension or low HDL colesterol, etc...

Lately the Steno Group and others has suggested that the link between microalbuminuria and cardiovascular disease may come from hypothesis that the existance of microalbuminuria means a general endothelial dysfunction and has its consequences not only in the glomerulus but also in the rethina, big vessels, etc...

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Microalbuminuria in type 1 diabetes

The presence of established microalbuminuria is associated with future development of diabetic nephropathy and with an increase risk of retinopathy, neuropathy and cardiovascular disease.

This is an independent association but may appear with other risk factors as hyperlipidemia or hypertension.

Approximately 25% of the patients has microalbuminuria 15 years after the diagnoses and often is associated with a hypertension history and a poor diabetic control beside other genetic factors not well defined at the present. There is a slight sex difference in the time that microalbuminuria develops, the average diabetes duration is 14 years for females and 16 years for males.

Almost 100 % of the type 1 patients with microalbuminuria during the first 10 years of diabetes well develop clinic diabetic nephopathy. By contrast only 50% of the patients with the first positive microalbuminuria appearing after 10 years of diagnoses will develop it.

Predicting factors of microalbuminuria in type 1 diabetes

It seems that the most important factor is the degree of diabetic control and it has been suggested a «critic level» of HB A1c for the appearance of the diabetic nephopathy and it was 8%.

In the following table we have summarired these predicting factors:

Microalbuminuria predicting factors in type 1 diabetes

- **Poor diabetes control.**
- **History of hypertension.**
- **Smoking habit.**
- **Hypertension family history.**
- **Insulin resistance.**
- **High LDL cholesterol.**
- **High renine plasmatic activity level.**
- **High plasmatic prorenine levels.**

Microalbuminuria in la type 2 diabetes

It has been clearly demostrated that the presence of microalbuminuria plays and independent role for the development of both, diabetic renal disease and cardiovascular disease.

In those type 2 microalbuminuria patient the mortality risk (mainly due to cardiovascular) is increase by 1.6 - 2.7 fold.

Recent studies has shown that they share the same risk of future development of macroproteinuria but the fact that only around 50% of the type 2 microalbuminuric patient arrives to the stage of renal failure is explained because the high cardiovascular mortality.

Recently it has been suggested by several studies that in the aged people the kidneys may respond differently to those in young people and with this theory will exist two different types of type 2 microalbuminuric patients because the typical diabetic glomeruloesclerosis is seen in just 50% of type 2 microalbuminuric patients and we don´t know yet if it means a different kidney disease prognoses.

Summary

An strict control of the blood pressure a better glycemic control, and reduction in the total daily protein intrake and posibly a change in the protein origin with a mandatory lifetime ACE inhibitors treatment are the best ways to delay the progression of the diabetic renal disease.

By checking microalbuminuria regularly to our diabetic patients we can positively improve their future.

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Glycosilated Hemoglobin

How important is it?

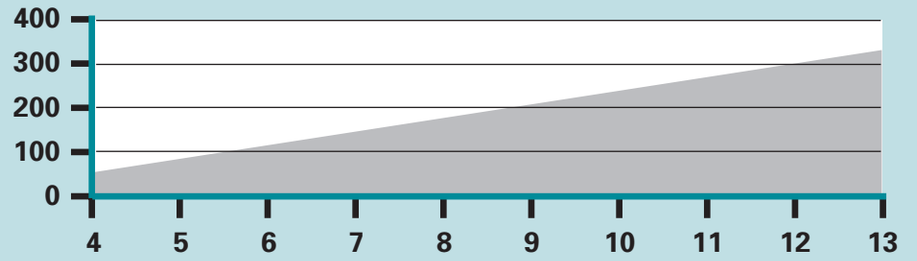
The Glycosilated Hemoglobin was discovered in 1958 by Allen later in 1966 was Hulsman the one that found out that there was some subfractions that were elevated in the diabetic patients. It was in 1975 when Tattersal discovered the correlation between HB A1c values and the glycemic control.

It is a well accepted fact since the findings of the DCCT study that quality of life of the person with diabetes depends primarily in the presence of late diabetic complications and the rate of appearance and progression of them is clearly linked to the degree of diabetes control. The HB A1c as a measure of the diabetes control is a key tool.

What is Glycosilated Hemoglobin?

Is the porcentage of the total haemoglobin linked to glucose molecules and this value depends on the average blood glucose levels.

Correlations between HbA_{1c} and average BG levels in the DCCT.



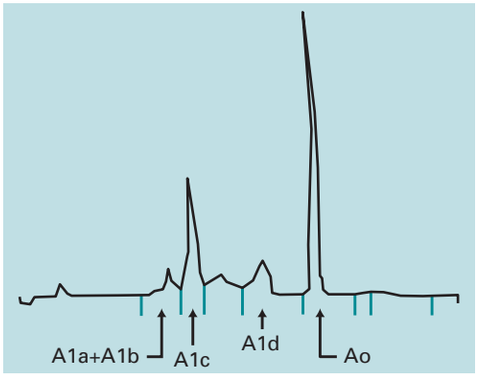
The Glycosilated Hemoglobin is formed as a result of non-enzimatic glycosilation, it is a process where the glucose is linked to some aminoacids of the haemoglobin molecule. This mechanism leads to the Amadori effect in wich is produced an stable product, the ketoamine that we usually know as Glycosilated Hemoglobin.

The Amadori phenomenon happens continuos and it is not reversible explaining why this union last during the remaining life of the red blood cell.

In the non-diabetic population the average blood glucose level is aproximately 100 mg % and that gives and HB A1c result around 5%.

What Hemoglobin types exists?

There are several haemoglobin types each one has different characteristics when linking to the glucose molecules. The hemoglobin A1 has three different subfractions a, b, and c. The union between the glucose and the c-subfraction of the HB A1 is more stable and specific and may gives a better information about the average glucose levels during the last 2-3 months.



Methods of Glycosilated Hemoglobin determination

There are four main measurement methods, electrophoresis, ionic-interchange chromatography, inmunoessay and affinity chromatography.

Electrophoresis and ionic-interchange chromatography both methods separates the haemoglobin types by their different changes, identyfying those haemoglobin molecules that during the glycosilation process has experimented a charge change (Hb A1 and Hb A1c).

The affinity chromatography separates the Glycosilated Hemoglobin from the rest of the hemoglobin by this method the total Glycosilated Hemoglobin is measured obviously the result will vary for each method because they measure different subfractions. The only way to compare results is when the method has been standarized to the interine reference method (DCCT BioRex 70). Every method has their own advantages and disadvantages and must be known in order to evaluate it correctly.

How to translate the Hb A1c values to glycemic control?

As we know the average span life of a red blood cell is 3 months and that is the reason why this lab test provides us with information about the degree of diabetic control during this period of time.

It is easy to understand that the Hb A1c result is not a just a simple average of blood glucose levels but a ponderate average and the results will be more related to the presance of more young red blood cells in the blood and generally is acepted that the last month contributes to 50% of the obtained result.

An increase of 1% in the Hb A1c value shows an increase of 30 mgrs. In the average glucose levels.

When and how must be measured?

The Hb A1c measurement can be made any time during the day regardless if you are fasting or not because obviously is independent of the glucose values in that moment.

Generally this test is done after a blood sample is taken from venupuncture but it can also be performed with a capilar blood sample the same way you do at home when you make a blood glucose test, with this method you and your diabetes healthcare team can know the results in several minutes.

Aditionaly there are several methods that allows you to do it at home with a capilar sample and send it by mail to your diabetes healtcare team for evaluation avoiding you to travel to your diabetes clinic.

How often is necessary to measure it?

The frequency of this lab test will vary depending upon your type of diabetes and the individual needs of every person with diabetes.

Generally speaking oral agents diabetic treated individuals will perform it at least twice in a year.

Insulin treated persons independently of their diabetes type will have their Hb A1c measured every 3 months.

Some special cases as the pregnant diabetes women will do it every month.

Which should be the Hgb A1c values goals?

Up to now a standarization of the Hb A1c has not yet been reached in spite of all the efforts made since 1986 when this program was launched. That is the reason why the results varies a lot between different methods and laboratories.

The National Glycohaemoglobin Standarization Group NGSP has the following goals:

- To establish if the proposed interin reference methods that was used in the DCCT Study, BioRex 70 is possible to be used as the primary reference system.
- To establish if it is posible to tranfer the reference method to other methods.

  One of the goals is to achieve the standarization of the majority of current and future determination methods to the DCCT method.
- Looking for the possibility to evaluate and preparate a primary calibration standard.

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It has been proposed that every manufacturer carries out the standarization process, with later verification in a «fresh sample» of the interine reference method DCCT/Goldstein BioRex 70. To date there are 10 standarized certified methods against the interine reference method.

Abbott IMX	**Bio-Rad HbA1c micro**
Bayer DCA 2000	**Bio-Rad Variant A1c**
Beckman Diatrac	**BMC Tina Quant**
Bio-Rad diamat	**Helena Gluyco-Tek**
Bio-Rad Diastat	**Primus HPLC**

The World Health Organization has proposed the following levels to evaluate the degree of diabetes control:

Ideal: < 6.5%	**Acceptable: 6.5 - 7.5%**	**Poor: > 7.5%**

In the patients with type 1 diabetes with C peptide negative is often not possible to achieve Hb A1c values similar to the non-diabetic population without provoking a non-aceptable high number of hypoglycemic episodies.

When you get very low Hb A1c values in these patients it is mandatory to rule out the presence of asymptomatic episodes of hypoglycemia often ocurring during the night.

By contrast in type 2 diabetes, specially in oral agents treated group often the Hb A1c values can be in the range of the non-diabetic population.

There is not any Hb A1c in the threshold for the complete prevention of the late diabetic complication but they are some studies suggesting a «critic level» corresponding to Hb a1c values over 8% when the increased risk is to high.

False results

Generally all the situations that may modify the red blood cell turnover will interfere with the Hb A1c results.

Bleedings, haemolitic anemias, splenectomy, uremia, high doses of aspirine or Vitamine C, high ethanol concentrations, lead intoxication, different haemoglobinpathies, etc...

All the mentionated circustances must be take into account when there are discrepancies between the expected Glycosilated Hemoglobin and the obtained result.

Lately with the newer methods like the high purificated liquid chromatography (HPLC) many of this problems are solved because they clearly separates the different hemoglobin subfractions.

Summary

Our main goal as a member of the diabetic healthcare team is to try to achieve the wellbeing of our patient with diabetes and maintain it in the future, because they are the most important members of all the diabetes health care team. Having it always in our minds will make mandatory to use all the available tools and surely the Glycosilated Hemoglobin is one of the most important because allows the patient to motivate themselves in the non-stop struggle that they do every day to keep healthy.

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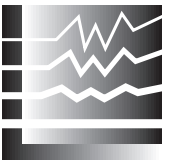

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