

## **Chapter 22: Diabetes, measurement of glycated haemoglobin and data from the Diabetic Registry**

Diabetic nephropathy is the single most common cause of renal failure in patients starting renal replacement therapy in the UK, where even so the incidence is lower than in most of the developed world. It is clearly important for the Registry to try to obtain more information on this condition. The UK Renal Registry and the United Kingdom Diabetic Analysis and Audit Service (UKDIABS) are exploring means of working together. This chapter contains the first results of such work. It comprises a joint analysis of data from the Diabetic Registry. In previous reports the Renal Registry has considered in some detail the problems of variations between clinical chemistry laboratories and the problems of harmonisation of data for comparison between units. This chapter includes a synopsis on methods of measurement of glycated haemoglobin in addition to current and future strategies on harmonisation of these results between hospitals. Some data from non-endstage patients from the UK diabetic registry is also included.

### **Summary**

#### **Summary on HbA1c standardisation**

- HbA1c measurements are an important outcome measure for both type I and type II diabetes mellitus, but techniques of measurement differ, and give varying results. Two very large clinical trials (DCCT and UKPDS) have shown that there is a powerful direct association between HbA1c levels and the risk of diabetic complications. HbA1c measurement systems have been 'standardised' through a process of 'alignment' of numerical results with the original DCCT method. This has been undertaken largely by the US National Glycohemoglobin Standardisation Program (NGSP) using a network of primary and secondary reference laboratories and a process of certification by means of a rigorous accuracy and precision protocol. In the UK, an expert panel published a consensus statement in 2000 that supported progress towards DCCT alignment of all methods used by UK laboratories, but indicated that a more rigorous scientific standardisation should be undertaken. About three quarters of UK laboratories have adopted DCCT aligned methods at the time of writing, many of whom were not-DCCT aligned prior to the Consensus Statement.
- Over the last five years, the International Federation of Clinical Chemistry (IFCC) Working Group on HbA1c Standardisation has created a true reference measurement system for HbA1c based on a re-definition of the chemical entity involved and a reference method. Comparison work has been undertaken with NGSP and the Swedish and Japanese standardisation programmes so that instrument and reagent manufacturers should be ready by the end of 2001 to release IFCC calibrants. It is anticipated that most currently non-DCCT aligned laboratories will adopt IFCC calibration, but those that are currently DCCT-aligned will have a difficult decision to make, as DCCT and IFCC numerical values are different. IFCC values are lower than DCCT below 8.5% HbA1c and greater than IFCC above this level. This change will require modification of the treatment outcome 'cut-off' levels based on DCCT and UKPDS, which clinicians are currently familiar with. The educational effort involved will be considerable. The National Service Framework for Diabetes development groups are aware of this situation.

## **Summary of UKDIABS data**

The UK Registry does not currently collect data on patients who are not receiving renal replacement therapy. The Renal Registry has liaised with the Diabetic Registry to analyse data from 47 district diabetic Registers included in the Diabetic Registry. Serum creatinine was measured at annual review in 56% of diabetic patients (range between centres 20 – 98%). From these measurements, 2.4% and 2.3% of Type 1 and Type 2 diabetics respectively had a serum creatinine > 200  $\mu\text{mol/L}$ . The proportion of patients in different centres with a serum creatinine > 200  $\mu\text{mol/l}$  varied from <1% to 9%.

The Cockcroft and Gault formula was used to calculate creatinine clearance. There is a strong relationship between the calculated creatinine clearance and both age of patient and length of time since diagnosed as diabetic. The relationship between blood pressure and renal impairment in Type 1 and Type 2 diabetics was examined. The only apparent association is between raised systolic blood pressure and renal failure in type I diabetics.

## **HbA1c Standardisation**

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### **Detailed description of the background to the current situation**

HbA1c - the major fraction of glycated haemoglobin (glycohaemoglobin in the US) that has glucose bound to the N-terminal valine of the  $\beta$ -chain - may be estimated by a number of different measurement principles: ion exchange chromatography, affinity chromatography and immunoassay. None of these method principles is truly specific for HbA1c; other glycated moieties co-elute or cross-react to some degree.

Until very recently (see below) scientifically correct standardisation of these measuring systems in terms of HbA1c was not possible, as neither a primary standard (pure HbA1c in a bottle) nor a reference method that could measure it without bias, existed.

Since the early 80's, pragmatic 'harmonisation' of results has been undertaken using the Goldstein ion exchange method (as a 'designated comparison method') that underpinned the 'HbA1c' measurements used in the 9 year Diabetes Control and Complications Trial (DCCT) of type I diabetics published in 1993. This showed that the risk for development and progression of the chronic complications of diabetes is closely related to the degree of glycaemic control, and it provided a large body of data relating 'HbA1c' values to mean blood glucose. These results set the stage for establishing specific diabetes treatment goals using 'HbA1c' as an index of mean blood glucose.

Because of the enormous impact of this trial, the American Diabetic Association set up a National Glycohaemoglobin Standardisation Programme (NGSP) to ensure that all measurement systems produced similar results. A core group of primary reference laboratories was established that maintained HbA1c results within strict limits of agreement with the 'original' DCCT ion-exchange method. To these was added a global network of secondary reference laboratories that use a variety of methods, but which are calibrated to agree within tight limits with the primary reference laboratories. Manufacturers may apply to an NGSP reference laboratory for NGSP certification of their methods, through successful completion of a strict accuracy and imprecision protocol.

Outside of the US other 'pragmatic harmonisation' systems have been developed in Sweden and Japan. In the UK, the recently published UK PDS Study confirmed the relationships between 'HbA1c' level and risk of complications for type II diabetics using methodology that was closely 'harmonised' with the 'DCCT method'. In the UK in 2000, an expert group published a consensus statement that supported the importance of DCCT harmonisation of HbA1c measurements, but which also indicated the need for a more rigorous scientific standardisation.

As stated in the first paragraph, NGSP 'harmonisation' can never be true standardisation, as no primary standards are involved in the process. (The 'original' 'DCCT method' was 'adjusted' by varying the temperature of the ion exchange column, for example.) Because the different 'HbA1c' measurement principles do not and cannot measure the same defined chemical entity, harmonisation is only achievable through the application of statistical regression 'factors' which 'align' the numerical results.

In the mid-90's, the International Federation of Clinical Chemistry (IFCC) set up an HbA1c Standardisation Working Group to establish a more scientifically based standardisation. They established a primary standard based on glycated and non-glycated hexapeptides cleaved from the  $\beta$ -chain (thus re-defining what HbA1c is), and a reference method procedure based on HPLC and either mass spectrometry or capillary electrophoresis. Comparison studies with the three main international systems (NGSP, Sweden & Japan) have been undertaken to establish the relationships between numerical values. During the coming year (2001), the information gained from these comparisons will be applied by manufacturers to develop calibrators for their assay systems that will enable HbA1c results to be expressed in terms of the new IFCC standards.

Although IFCC standardisation is scientifically correct, its application will mean that numerical values for HbA1c measurements will change. The regression slope of DCCT vs IFCC is about 0.76 with an intercept of about 2% HbA1c. This means that below about 8.5% HbA1c (normal to fairly well controlled levels), IFCC results will be lower than DCCT, and above 8.5% (increasingly poor control) IFCC results will be higher. Clinicians who use DCCT/UKPDS treatment outcome levels will have to adjust their decision points accordingly. Because of the weight of the medical evidence base, the educational effort involved will be enormous (it would be impossibly expensive to repeat the two trials using IFCC standardised methods). The committees of the UK National Service Framework (NSF) for diabetes are currently considering the impact of this situation. Because the US has invested huge resources in promoting and maintaining DCCT harmonisation through NGSP, they may not accept IFCC standardisation directly and might attempt to re-calculate IFCC results in terms of DCCT. This will place considerable pressure on US based manufacturers who may have to offer different regional calibrators.

In summary, then, we have a fierce '*true scientific*' vs a '*pragmatic clinical approach*' debate in progress.

Do we change medical decision limits that are supported by a huge evidence base because the numerical values produced by the original and NGSP harmonised methods are wrong and have to be re-evaluated using a true accuracy base?

The UK NEQAS service for HbA1c is helping laboratories understand this situation and come to a decision about how their service should be standardised, by providing individual method

and calibration strategy means and both DCCT and IFCC reference method target values for all materials distributed.

#### **Sources / further information**

- DCCT & NGSP : <http://web.missouri.edu/~diabetes/ngsp/index.html>
- UKPDS : <http://www.dtu.ox.ac.uk/index.html?maindoc=/ukpds/>
- UK Consensus statement : Marshall SM and Barth JH. Standardization of HbA1c measurements: a consensus statement. *Ann Clin Biochem* 2000;37:45-46
- IFCC :<http://www.ifcc.org> and <http://web.missouri.edu/~diabetes/ngsp/IFCCWG.html>

## ***UK Diabetic Registry***

### ***Overview of the UK Diabetic Registry***

In September 1996 the UKDIABS project was initiated at the British Diabetic Association, with the aim of providing an audit and benchmarking service to districts and clinicians who had local databases of clinical information about people with diabetes. The main objective of the project was to enable quality improvement of diabetes services through better monitoring of clinical care.

The project collects data from districts, either through a standardised download (available as part of the standard software on the great majority of Diabetes Information Systems), or through working with local systems to obtain a usable data set for audit.

These data are, as far as possible, standardised on the UK recommended diabetes dataset. They can display variations in diabetes incidence and outcomes, as well as provide some information about local variations in care provision. Results are fed back to local districts in a benchmarking exercise, to inform local care providers about their services, and to assist local quality development. For 1997 and 1998 respectively there are about 102,000 and 155,000 patient records contained within UKDIABS. For 1998 this translates into data on 22% of all UK diabetics who had a medical contact in that year.

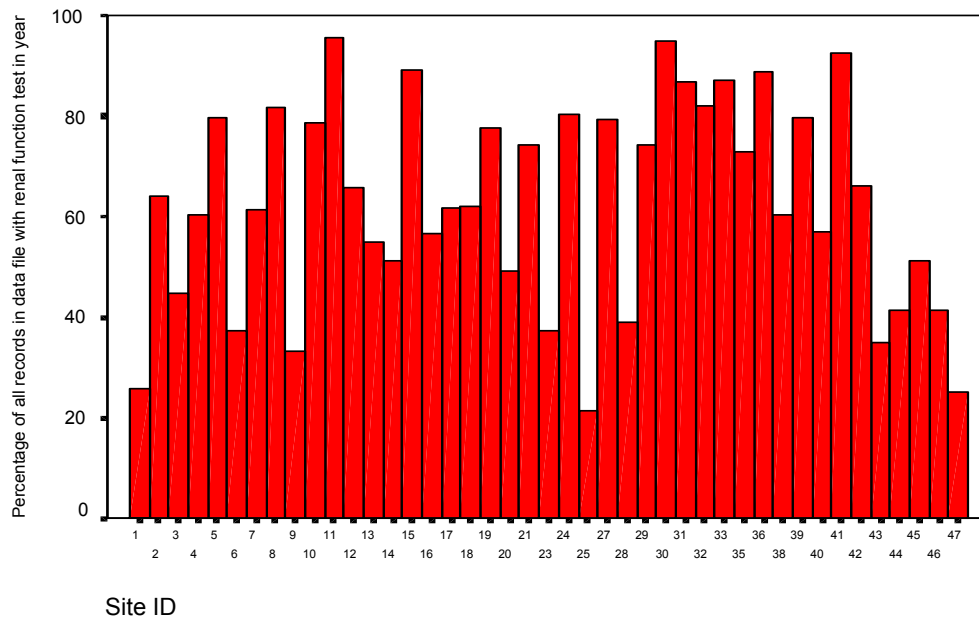
### ***Diabetic dataset***

- 8 demographic fields
- 27 true outcome measures
- 27 indicators of adverse outcomes
- 8 risk factors for adverse outcome
- 6 metabolic outcomes
- 4 health satisfaction fields
- 3 local use fields

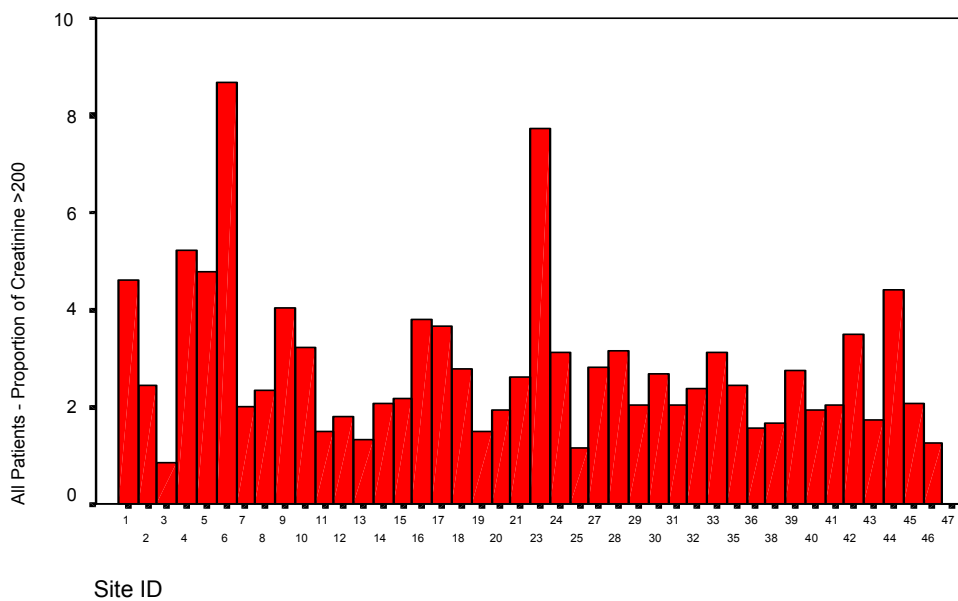
## Results

Using data amalgamated from 47 district diabetic Registers, 56% (range 20 –98%) had a creatinine measured at annual review. Of those patients, 2.4% and 2.3% of Type 1 and Type 2 diabetics respectively had a creatinine > 200  $\mu\text{mol/L}$ .

Figures 22.1 and 22.2 indicate by Centre the percentage of patients in whom serum creatinine was measured at annual review, and the proportion of patients in whom the creatinine was >200 $\mu\text{mol/l}$ . The low rate on creatinine monitoring is disappointing.



**Figure 22.1** The proportion of patients with a creatinine measured at annual review

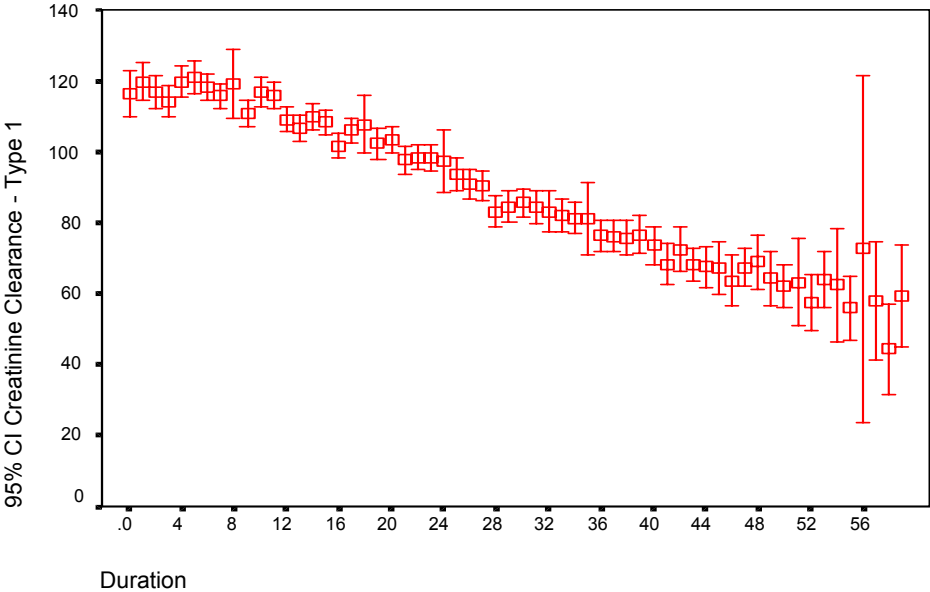


**Figure 22.2** The percentage serum creatinine measurements > 200 $\mu\text{mol/l}$

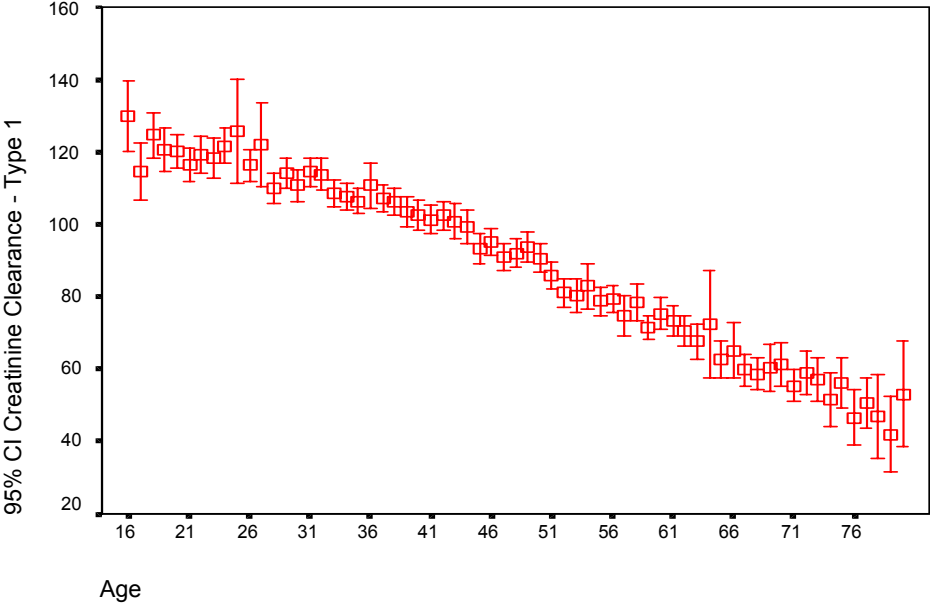
Centres 25 and 47, with two of the lowest rates of measurement of renal function (20%) also have the lowest percentage of tested patients with a creatinine > 200 umol/L. This contrasts with centre 6 where only 36% of patients have a creatinine measured but almost 9% of these results are above 200 umol/L.

**Creatinine clearance**

Figures 22.3 to 22.6 show renal function in relation to duration of diabetes and age. Creatinine clearance has been calculated using the Cockcroft and Gault method. The lines indicated the 95% confidence intervals.

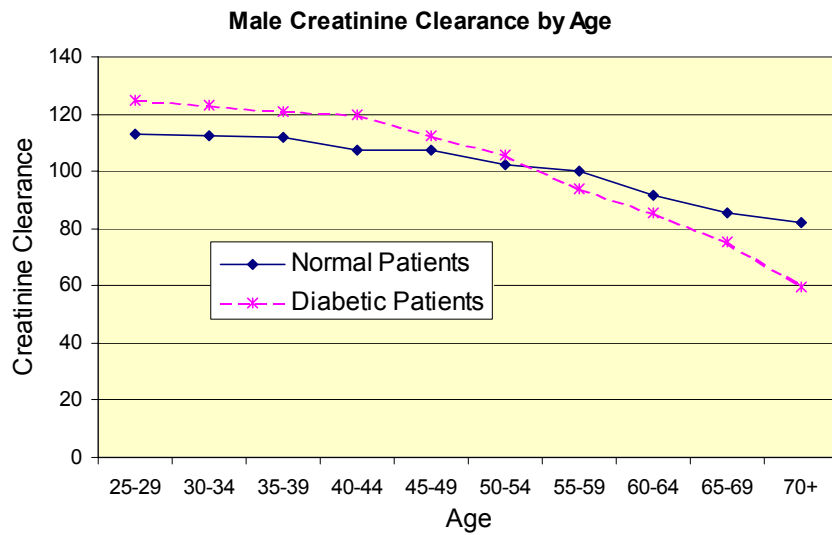


**Figure 22.3** Calculated creatinine clearance and duration of diabetes – type I diabetics.

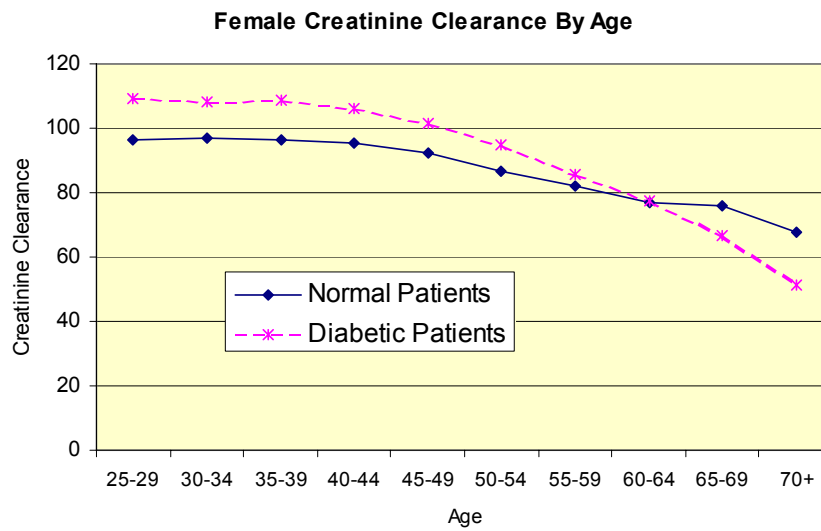


**Figure 22.4** Calculated creatinine clearance and age – type I diabetics.

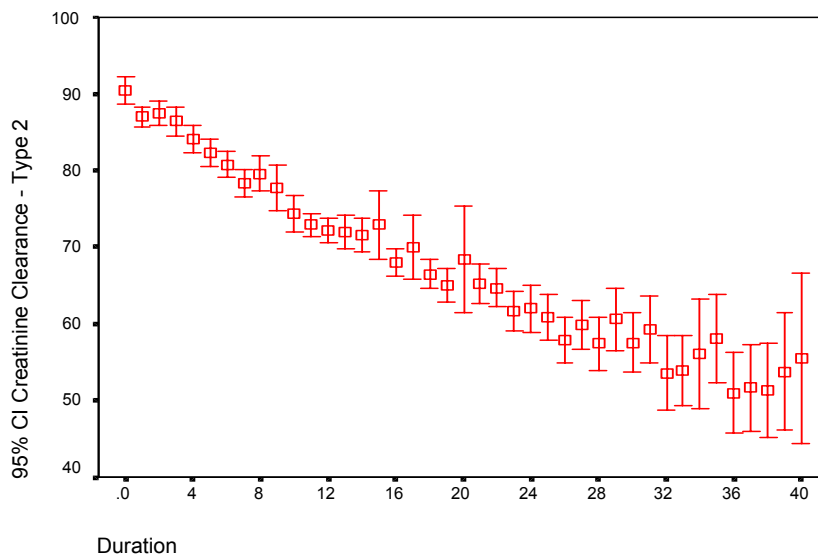
These data are very similar to the normal population and this is shown in the figures 22.5-6



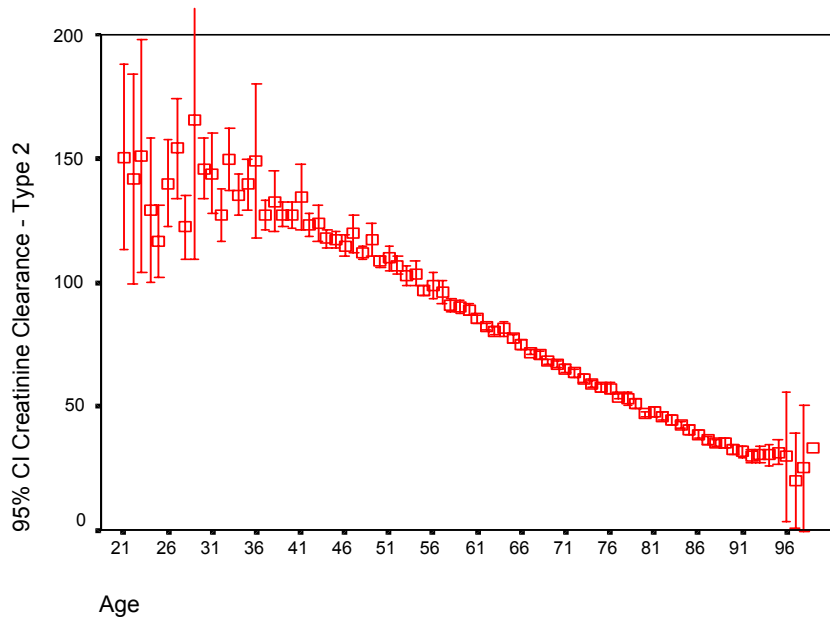
**Fig 22.5 Decline in creatinine clearance in diabetics v non-diabetic males**



**Fig22.6 Decline in creatinine clearance in diabetics v non-diabetic females**



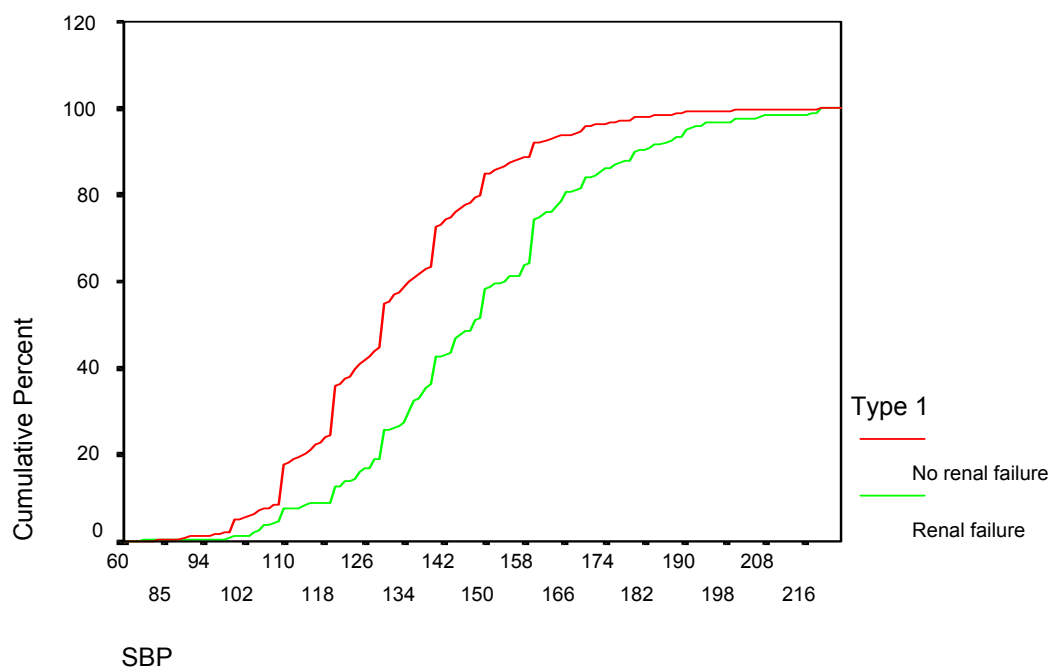
**Figure 22.7 Calculated creatinine clearance and duration of diabetes – type II diabetics.**



**Figure 22.8** Calculated creatinine clearance and age – type II diabetics.

The wide confidence limits at the ends of the spectrum are attributable to the small number of observations at these points.

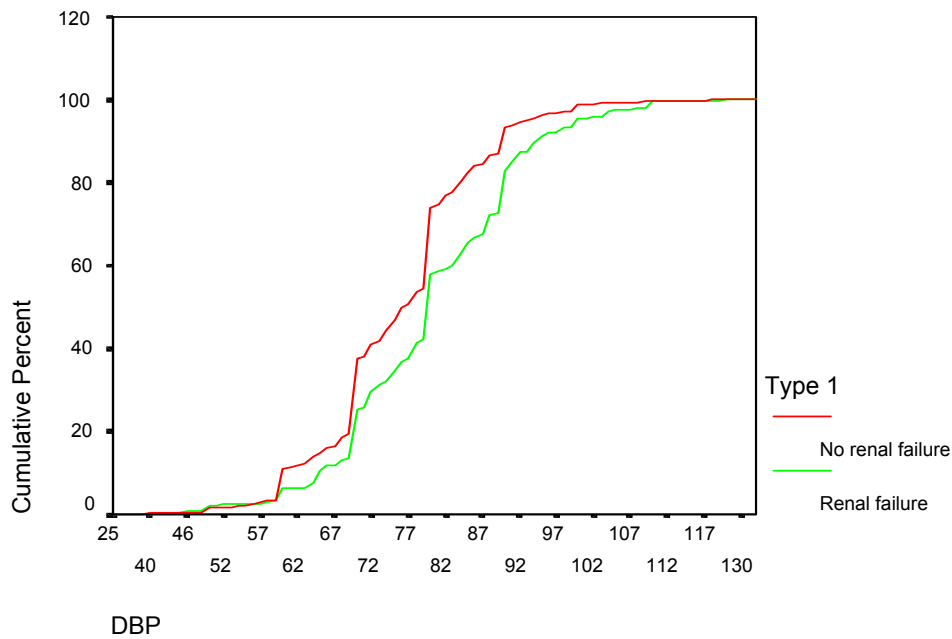
*Renal impairment and blood pressure in Type 1 diabetics*



n = 11,088 -no renal impairment,  
n = 241 renal impairment

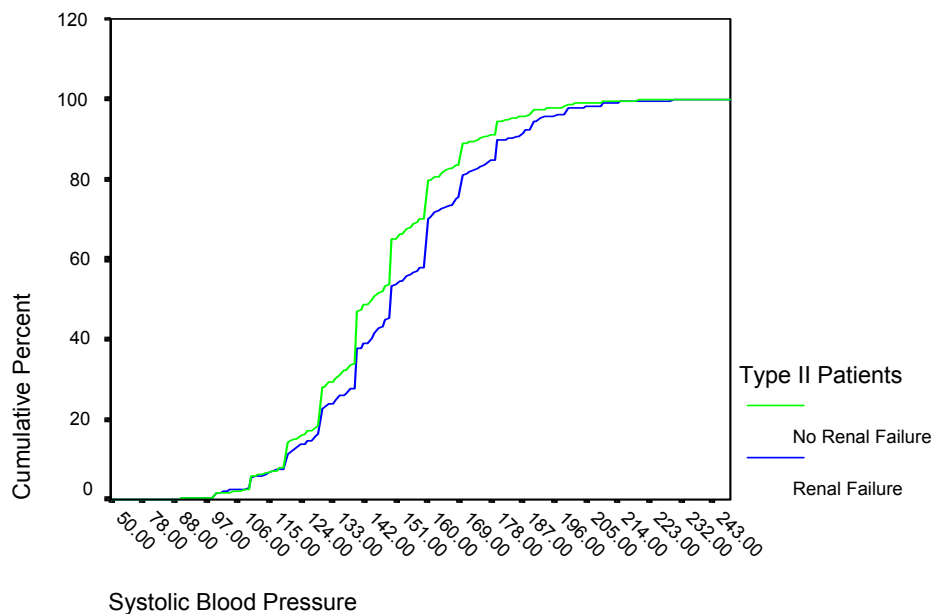
**Figure 22.9** Systolic blood pressure and renal impairment in Type1 diabetics





**Figure 22.10 Association between diastolic BP and renal impairment in type I diabetics.**

In Type 1 diabetics, the relationship between the incidence of renal impairment and elevated blood pressure was strong for the systolic pressure but weak for the diastolic pressure.



Type 2 diabetics  
 n= 63,750 – no renal failure  
 n= 1,100 – renal failure

**Figure 22.11 The relationship between renal impairment and systolic blood pressure in type II diabetics.**

The data presented here are cross-sectional and do not relate sequentially to individual patients. It is intended to develop a close working relationship between the two registries to create a complete longitudinal dataset for diabetic patients with renal impairment, with which it will be possible to monitor the progress of individuals and track changes which may eventually lead to renal failure.