group was restricted to normoglycemic individuals >60 years of age to minimize inclusion of those likely to develop type 2 diabetes later in life. In addition, P12A genotyping was also performed on a random sample of 727 Saudi neonatal bloodspots to ascertain P12A allele frequencies in an unbiased sample.

Data analysis was first performed for an age- and sex-matched cohort in which the type 2 diabetic cases ($n$ = 118) and control subjects ($n$ = 219) were >60 years old. The male-to-female ratios of these case and control subjects were 1.40 and 1.43, respectively. The *P*, or risk allele, frequency was 0.974 and 0.968 in type 2 diabetic and control subjects, respectively, and was not statistically significant ($P$ = 0.633). However, given the very high incidence of the *P* allele in this population, the study size was extremely underpowered. No age-related differences in P12A allele frequencies were observed. Demonstration of statistical significance or lack thereof in the Saudi population, at a 95% CI or better, is impractical, as this would require case and control populations where $n$ is >175,000. The high incidence of the *P* allele in the Saudi population was confirmed by the neonatal sample set in which frequency of this allele was found to be 0.957. Clearly the risk allele frequency of the Saudi population is comparable to the Japanese, Chinese, and African Americans and is among the highest observed to date.

SALMA M WAKIL, PHD[1]
KHALID AL-RUBEAAN, MD, FRCP(C)[2]
OSAMA ALSMADI, PHD[1]
FAIQA IMTIAZ, PHD[1]
PAMELA CARROLL, BSC[1]
MOHAMMED RAJAB, BSC[1]
SHADEN AL-KATARI, MD[2]
MOHAMMED AL-KATARI, MD[2]
BRIAN F. MEYER, PHD[1]

From the [1]Aragene Laboratory, Research Centre, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; and the [2]Diabetes Center, King Abdulaziz University Hospital, Riyadh, Saudi Arabia.

Address correspondence to Khalid Al-Rubeean, MD, FRCP(C), Diabetes Center, KAUH, Riyadh 18397, Saudi Arabia 11415. E-mail: krubean@ksu.edu.sa.



**References**

1. Altshuler D, Hirschhorn JN, Klannemark M, Lindgren CM, Vohl MC, Nemesh J, Lane CR, Schaffner SF, Bolk S, Brewer C, Tuomi T, Gaudet D, Hudson TJ, Daly M, Groop L, Lander ES: The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet* 26:76–80, 2000
2. Celi FS, Shuldiner AR: The role of peroxisome proliferator-activated receptor gamma in diabetes and obesity. *Curr Diab Rep* 2:179–185, 2002

# The Application of Synthetic hANP in Diabetic Nephropathy With Nephrotic Syndrome

Although the optimal time to initiate hemodialysis is not well defined, it is necessary to start extracorporeal ultrafiltration methods (ECUM) earlier in uremic diabetic patients to avoid life-threatening events, such as anasarca, heart failure, and lung congestion. These patients frequently manifest the poor response to the administration of high dosage of loop diuretics. To investigate the effectiveness of concomitant usage of synthetic human atrial natriuretic peptide (hANP) with loop diuretics, we administered carperitide (hANP) in a case with diabetic nephropathy and nephrotic syndrome.

A 44-year-old woman with 10-year history of type 2 diabetes was referred to our hospital because of oliguria, generalized edema, repeated vomiting, and severe diarrhea. She developed overt proteinuria 3 years ago and has been treated with glimepiride. She presented severe anasarca and gained >15 kg body wt during the past 2 months. Blood pressure was 147/87 mmHg, and Achilles tendon reflex and vibrating sense of lower extremities disappeared. She had diabetic retinopathy and received photocoagulation 3 years before. Serum albumin was 1.9 g/dl, serum creatinine 1.92 mg/dl, total cholesterol 419 mg/dl, daily urinary protein secretion 12.4 g, and creatinine clearance 18.4 ml/min. Cardio-thoracic ratio was 51% in chest X-ray, and pleural effusion and ascites were seen in computed tomography. We started oral and intravenous administration of furosemide (200 mg/day) and infusion of albumin. However, she became anuric at the 7th hospital day, 250–300 ml/day. Before we performed ECUM, we started continuous infusion of carperitide from a dose of 0.025 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and maintained at 0.08 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The concomitant use of furosemide brought prominent diuresis reaching 2,000 ml/day, and we gradually tapered the dosage and continued for 25 days. Finally, she maintained the daily urine volume of 1,000–1,500 ml/day with the oral administration of furosemide (120 mg/day) without deterioration of renal functions. Edema, ascites, vomiting, and diarrhea disappeared, and her body weight returned to 56 kg (Fig. 1).

Although the remission and regression of nephrotic syndrome due to diabetic nephropathy was reported (1), the massive proteinuria is usually intractable, and most patients finally manifested end-stage renal disease. The use of a high dosage of diuretics also accelerates intravascular dehydration, elevation of creatinine and uric acid levels, and impaired renal function. Synthetic hANP elevates glomerular filtration rate by increasing renal blood flow and relaxation of the mesangial cells. It also increases the medullary blood flow and inhibits reabsorption of sodium and water of collecting duct cells. The concomitant use of synthetic hANP and loop diuretics enhances the diuretic action and may suppress furosemide-induced aldosterone activation (2). Instead of ECUM, the administration of synthetic hANP in nephrotic patients with diabetic nephropathy is useful to avoid life-threatening anasarca and may prevent the progressive deterioration of renal function.

YOKO KIKUMOTO, MD
JUN WADA, MD, PHD
HIROFUMI MAKINO, MD, PHD

From the Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Okayama, Japan.

Address correspondence to Jun Wada, MD, PhD, Assistant Professor, Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, 2-5-1 Shikata-cho, Okayama 700-8558, Japan. E-mail: junwada@md.okayama-u.ac.jp.



**References**

1. Hovind P, Tarnow L, Rossing P, Carstensen B, Parving HH: Improved survival in patients obtaining remission of nephrotic range albuminuria in diabetic nephropathy. *Kidney Int* 66:1180–1186, 2004
2. Cataliotti A, Boerrigter G, Costello-Boerrigter LC, Schirger JA, Tsuruda T, Heublein DM, Chen HH, Malatino LS, Burnett JC Jr: Brain natriuretic peptide en-

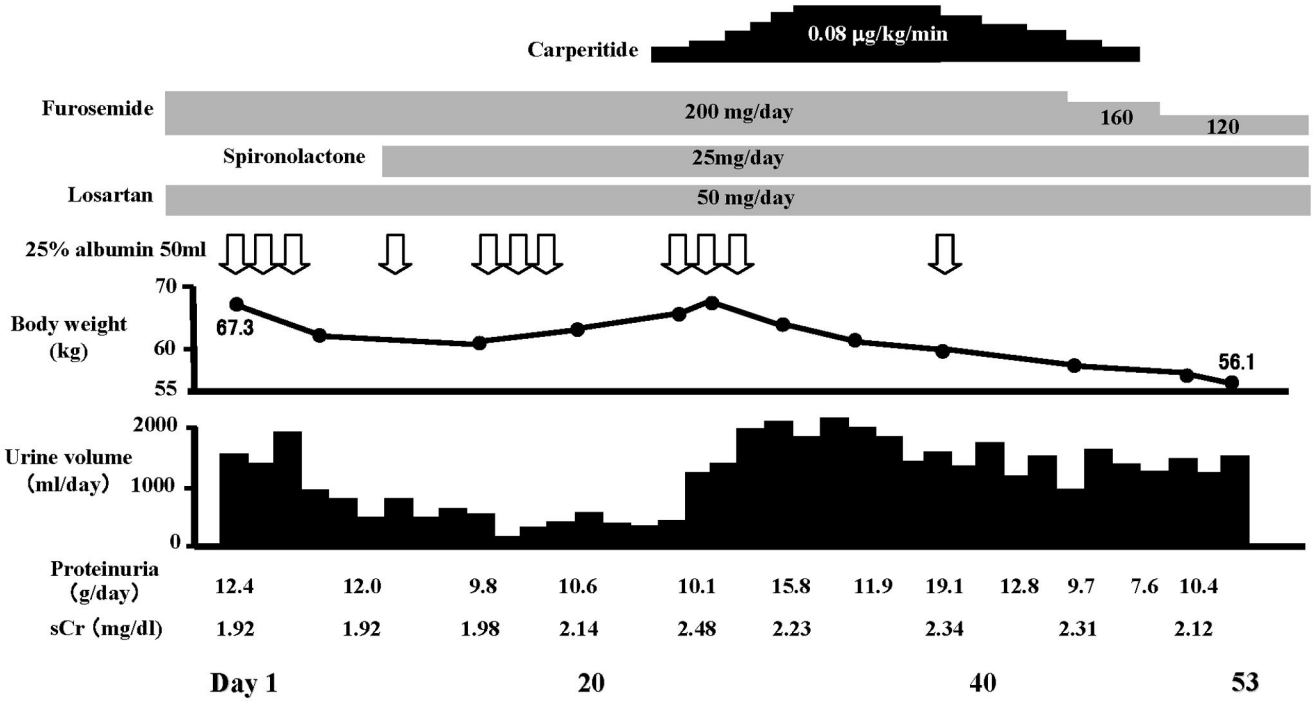


**Figure 1—***The clinical course of the case.*

hances renal actions of furosemide and suppresses furosemide-induced aldosterone activation in experimental heart failure. *Circulation* 109:1680–1685, 2004

# Seasonality in the Incidence of Type 2 Diabetes

## A population-based study

The seasonal pattern in the onset of type 1 diabetes has been described (1), but seasonality in the onset of type 2 diabetes has not been previously reported. Some studies revealed seasonal changes in glycemic control in selected cohorts of patients with type 2 diabetes (2–4). While the incidence of type 1 diabetes can be easily studied based on complete registries, the onset of type 2 diabetes is more difficult to identify and study because in the earliest stage of the disorder, mostly nonmedical approaches are applied that are not always recorded in the medical profile. In the progression of type 2 diabetes, the initiation of treatment with oral antihyperglycemic drugs is the stage at which all patients can be definitively recognized as having the disorder.

We identified all incident cases of type 2 diabetes ($n$ = 26,695) for the entire population of Csongrád County, Hungary ($n$ = 430,000), between January 1999 and December 2004. Information was retrieved from the database of the Hungarian National Health Fund Administration, which provides a complete history of prescription drug use of the population at the patient level. Incident cases were defined as patients who had received no antidiabetic therapy during the 12-month period prior the initiation of an oral antihyperglycemic drug.

For quantifying the strength of seasonality, an autoregressive regression model was fitted to the monthly data and the coefficient of determination ($R^2_{\text{Autoreg}}$) calculated (5). The results of the regression revealed a strong seasonality ($R^2_{\text{Autoreg}}$ = 0.632). Seasonality followed a sinusoidal pattern; the peak month was March, with a monthly incidence of 430.3 ± 34.0 (means ± SD) cases, and the trough month was August, with a monthly incidence of 293.2 ± 23.8 cases. Similar patterns were found in both sexes. The months of peak and trough coincide with the peak and trough periods in the seasonality of $HbA_{1c}$ values previously reported (2).

**Péter Doró, mpharm**
**Ria Benkő, mpharm**
**Mária Matuz, mpharm**
**Gyöngyvér Soós, phd**

From the Department of Clinical Pharmacy, University of Szeged, Szeged, Hungary.

Address correspondence to Péter Doró, Szikra u.8., Szeged, H-6725, Hungary. E-mail: dorop@clph.szote.u-szeged.hu.



**References**

1. Karvonen M, Jantti V, Muntoni S, Stabilini M, Stabilini L, Muntoni S, Tuomilehto J: Comparison of the seasonal pattern in the clinical onset of IDDM in Finland and Sardinia. *Diabetes Care* 21:1101–1109, 1998
2. Tseng CL, Brimacombe M, Xie M, Rajan M, Wang H, Kolassa J, Crystal S, Chen TC, Pogach L, Safford M: Seasonal patterns in monthly hemoglobin A1c values. *Am J Epidemiol* 161:565–574, 2005
3. Sohmiya M, Kanazawa I, Kato Y: Seasonal changes in body composition and blood $HbA_{1c}$ levels without weight change in male patients with type 2 diabetes treated with insulin. *Diabetes Care* 27:1238–1239, 2004
4. Ishii H, Suzuki H, Baba T, Nakamura K, Watanabe T: Seasonal variation of glycemic control in type 2 diabetic patients (Letter). *Diabetes Care* 24:1503, 2001
5. Moineddin R, Upshur R, Crighton E, Mamdani M: Autoregression as a means of assessing the strength of seasonality in a time series. *Popul Health Metr* 1:10, 2003