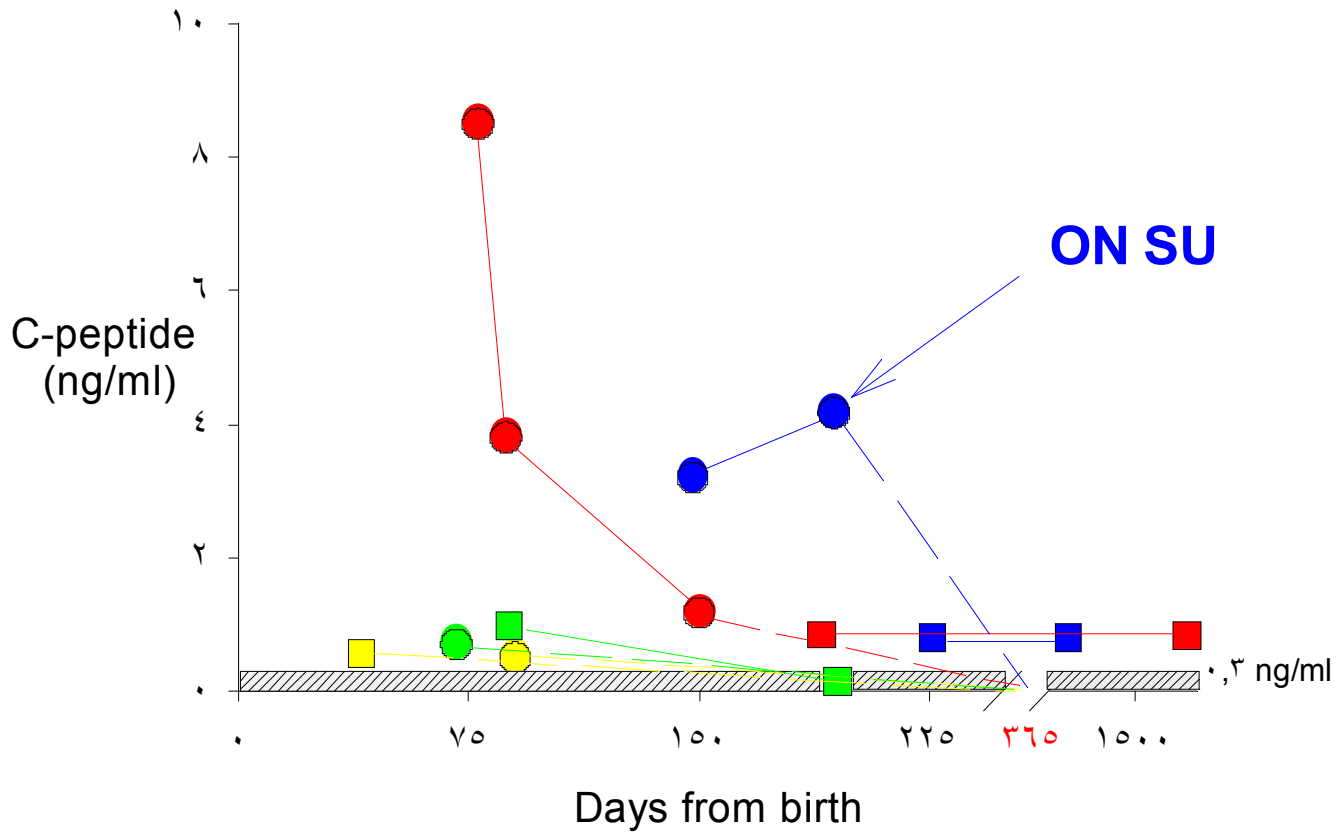


	B-chain	C - peptide	A-chain
Homo Sapiens	FVNQH <b>CGSH</b> VEALYLV <b>GERGFFY</b> TPKT-	REAEDLQVGQVELGGGPGAGSLQPLALEGS--LQ <b>KR</b>	<b>GIVEQCC</b> TSI <b>CSLYQLENYCN</b>
Rattus Norvegicus	FVKQH <b>CGSH</b> VEALYLV <b>GERGFFY</b> TPMS-	REVEDPQVAQLELGGGPGAGDLQTLALEVA--RQ <b>KR</b>	<b>GIVDQCC</b> TSI <b>CSLYQLENYCN</b>
Mus Musculus	FVKQH <b>CGPH</b> VEALYLV <b>GERGFFY</b> TPKS-	REVEDPQVEQLELGGSP--GDLQTLALEVA--RQ <b>KR</b>	<b>GIVDQCC</b> TSI <b>CSLYQLENYCN</b>
Gallus Gallus	--NQH <b>CGSH</b> VEALYLV <b>GERGFFY</b> SPKA-	RDVEQPLVSSPLRG---EAGVLPFQQEYE--KV <b>KR</b>	<b>GIVEQCCH</b> NT <b>CSLYQLENYCN</b>
Xenopus Tropicalis	--NQH <b>CGSH</b> VEALYLV <b>GD</b> RGFFYYPKI-	KRDIEQAMVNGPQDN---ELDGMQLQPQEQ--KM <b>KR</b>	<b>GIVEQCCH</b> ST <b>CSLFQLESYCN</b>
Danio Rerio	--SQH <b>CGSS</b> VDALYLV <b>GP</b> RGFFYTNRG-	RDLETLLALLSNLAGYEAADA-DPLKEKVM--KM <b>KR</b>	<b>GIVEQCCH</b> RPCTIYH <b>LEDYCS</b>
Myxine Glutinosa	----H <b>CGKD</b> LVNALYI <b>AG</b> VRGFFYDPTKM	KRDTGALAAFLPLAYAEDNESQDDESIGINEVLK <b>SKR</b>	<b>GIVEQCCH</b> KR <b>CSIYDLENYCN</b>

- |   |  |   |   |
|---|--|---|---|
| ● Kindred A (nd-PS/ $\wedge$ )<br>R $\wedge$ =C | ● Kindred C (nd-VI/ $\wedge$ )<br>R $\wedge$ =C  | ● Kindred E (nd-PD/ $\wedge$ )<br>L $\wedge$ <sup>B<math>\wedge</math></sup> P        | ● Kindred H (nd-CO-LE/ $\wedge$ )<br>L $\wedge$ <sup>B<math>\wedge</math></sup> P |
| ■ Kindred B (nd-FI/ $\wedge$ )<br>R $\wedge$ =C | ■ Kindred D (nd-BO/ $\wedge$ )<br>L $\wedge$ <sup>B<math>\wedge</math></sup> $\gamma$ B $\wedge$ <sup>B<math>\wedge</math></sup> delinsH | ■ Kindred F (nd-PI/ $\wedge$ )<br>C $\wedge$ <sup>A<math>\wedge</math></sup> $\gamma$ | ■ Kindred I (nd-NO/ $\wedge$ )<br>L $\wedge$ <sup>B<math>\wedge</math></sup> V    |



Supplemental figure 1. Insulin sequences from homo sapiens down to mixine glutinosa (hagfish) are aligned. In red: invariant residues. Invariant cysteines are highlighted in dark blue. Leucines in position 6 and 11 of the human insulin b-chain, found mutated in patients with PNDM-MDI, are highlighted in bright green.

Supplemental figure 2. C-peptide levels in patients with PNDM-MDI from the diagnosis of diabetes and the following months. This figure shows in a graphical form the data reported in Table 1. Please note that the second c-peptide determination of kindred H has been performed while the patient was on treatment with sulfonylurea (SU).