ΕΛΛΗΝΙΚΑ
ΔΙΑΒΗΤΟΛΟΓΙΚΑ
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ΟΡΓΑΝΟ ΤΗΣ ΕΛΛΗΝΙΚΗΣ ΕΤΑΙΡΕΙΑΣ ΜΕΛΕΤΗΣ ΚΑΙ ΕΚΠΑΙΔΕΥΣΗΣ ΓΙΑ ΤΟΝ ΣΑΚΧΑΡΩΔΗ ΔΙΑΒΗΤΗ

PROCEEDINGS OF THE 1ST JOINT INTERNATIONAL MEETING

"DIABETES MELLITUS. FROM BASIC RESEARCH TO THE DAY-TO-DAY CLINICAL PRACTICE"

Co-organized by the Department of Internal Medicine IV, University of Tübingen and the Institute for Diabetes, Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, along with the Hellenic Association for the Study & Education of Diabetes Mellitus

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ΕΛΛΗΝΙΚΑ ΔΙΑΒΗΤΟΛΟΓΙΚΑ ΧΡΟΝΙΚΑ

Τριμηνιαία έκδοση
της Ελληνικής Εταιρείας Μελέτης και Εκπαίδευσης για τον Σακχαρώδη Διαβήτη
(πρώην Δ.Ε.Β.Ε.)

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ΟΔΗΓΙΕΣ ΠΡΟΣ ΤΟΥΣ ΣΥΓΓΡΑΦΕΙΣ

Στα «*Ελληνικά Διαβητολογικά Χρονικά*» της **Ελληνικής Εταιρείας Μελέτης και Εκπαίδευσης για τον Σακχαρώδη Διαβήτη** (προηγούμενη ονομασία Διαβητολογική Εταιρεία Βόρειας Ελλάδας – ΔΕΒΕ) δημοσιεύονται εργασίες που έχουν διαβητολογικό ενδιαφέρον με κύριο σκοπό την ιατρική εκπαίδευση και επιμόρφωση ιατρών, νοσηλευτών και φοιτητών. Οι εργασίες που δημοσιεύονται ακολουθούν συγκεκριμένη δομή και ανήκουν σε ορισμένους τύπους άρθρων.

Όλα τα άρθρα πρέπει να συνοδεύονται στα **Ελληνικά** και **Αγγλικά** από τα ονόματα συγγραφέων, τον τίτλο του άρθρου, την περίληψη και τις λέξεις-κλειδιά. Εξαίρεση αποτελούν τα «Εκπαιδευτικά άρθρα» τα οποία δεν συνοδεύονται από περίληψη ούτε από βιβλιογραφία, καθώς και οι «Ενδιαφέρουσες δημοσιεύσεις».

ΕΙΔΗ ΑΡΘΡΩΝ ΠΟΥ ΔΗΜΟΣΙΕΥΟΝΤΑΙ ΣΤΟ ΠΕΡΙΟΔΙΚΟ

Άρθρα της σύνταξης: Γράφονται από τον διευθυντή σύνταξης του περιοδικού ή από άλλο πρόσωπο μετά από σχετική ανάθεση που του κάνει ο διευθυντής σύνταξης ή ο πρόεδρος ή το ΔΣ της Ελληνικής Εταιρείας Μελέτης και Εκπαίδευσης για τον Σακχαρώδη Διαβήτη με απόφασή του. Δεν υπερβαίνουν τις δυο σελίδες.

Ανασκοπήσεις: Γράφονται κατά προτίμηση από έναν/μία συγγραφέα, κατ' εξαίρεση από δύο ή τρεις, ιδίως όταν το θέμα απαιτεί συγγραφείς διαφορετικών ειδικοτήτων. Η έκταση του άρθρου πρέπει να είναι 15 έως 25 σελίδες στις οποίες περιλαμβάνονται η εικονογράφηση, η βιβλιογραφία και στα Ελληνικά και Αγγλικά: η περίληψη, οι λέξεις-κλειδιά, οι συγγραφείς και ο τίτλος του άρθρου.

Επίκαιρα θέματα: Το αντικείμενο των άρθρων της κατηγορίας αυτής μπορεί να είναι διαγνωστικού ή θεραπευτικού περιεχομένου ή και να αφορά οποιονδήποτε τομέα της ιατρικής επιστήμης. Γράφονται για να κάνουν ευρύτερα γνωστό ένα πρόσφατο επίτευγμα στον τομέα που έχουν επιλέξει οι συγγραφείς.

Η έκταση του άρθρου πρέπει να περιορίζεται σε 4-6 περίπου σελίδες με 10-15 βιβλιογραφικές παραπομπές.

Πρωτότυπες εργασίες: Έχουν κλινικό ή εργαστηριακό ή κλινικοεργαστηριακό περιεχόμενο. Το κείμενο περιλαμβάνει βραχεία εισαγωγή, όπου αναφέρεται ο σκοπός της εργασίας, περιγραφή του υλικού και των μεθόδων, έκθεση των αποτελεσμάτων, συζήτηση στην οποία περιλαμβάνονται και τα τελικά συμπεράσματα. Η περίληψη πρέπει να είναι αυτοτελής και να περιέχει τον σκοπό της εργασίας, τις βασικές μεθόδους που χρησιμοποιήθηκαν, τα κύρια ευρήματα και τα σημαντικότερα συμπεράσματα. Η έκταση του άρθρου δεν πρέπει να υπερβαίνει τις 14 σελίδες, μαζί με τη βιβλιογραφία.

Ενδιαφέρουσες περιπτώσεις: Σ' αυτές παρουσιάζονται ενδιαφέρουσες ή σπάνιες περιπτώσεις με κλινικές εκδηλώσεις που περιγράφονται για πρώτη φορά, ή περιπτώσεις με ιδιαίτερη ατυπία, καθώς και άλλες στις οποίες χρησιμοποιήθηκαν νέες διαγνωστικές ή θεραπευτικές μέθοδοι ή διατυπώνονται νέες απόψεις για την παθογένειά τους.
Έχουν έκταση έως 5 σελίδες και περιλαμβάνουν σύντομη εισαγωγή, περιγραφή της περιπτώσεως, πίνακες ή εικόνες (έως 4), τα κύρια εργαστηριακά ευρήματα, βραχύ σχόλιο-συζήτηση, περιορισμένη βιβλιογραφία (10-15 παραπομπές).

Επιστολές προς τη Σύνταξη: Περιέχουν κρίσεις για δημοσιευμένα άρθρα, παρατηρήσεις για ανεπιθύμητες ενέργειες φαρμάκων, κρίσεις για το περιοδικό κ.τ.λ. Η έκτασή τους δεν υπερβαίνει τις 400 λέξεις. Ο αριθμός των βιβλιογραφικών παραπομπών δεν πρέπει να υπερβαίνει τις οκτώ.

Εκπαιδευτικά άρθρα: Πρόκειται για σύντομα άρθρα (4-5 σελίδων) που αποσκοπούν στη βασική διαβητολογική εκπαίδευση νέων γιατρών ή φοιτητών. Δεν συνοδεύονται από περίληψη ούτε από βιβλιογραφία.

Ενδιαφέρουσες δημοσιεύσεις: Κατόπιν προσκλήσεως ανατίθεται σε μέλος της εταιρείας να παρουσιάσει τα με ιδιαίτερο ενδιαφέρον αποτελέσματα ερευνών, τα οποία έχουν προσφάτως δημοσιευτεί σε έγκριτα περιοδικά ή ανακοινώθηκαν σε μεγάλα συνέδρια.

ΤΡΟΠΟΣ ΥΠΟΒΟΛΗΣ ΚΑΙ ΔΙΑΔΙΚΑΣΙΑ ΔΗΜΟΣΙΕΥΣΗΣ

Όλα τα άρθρα υποβάλλονται στο ηλεκτρονικό ταχυδρομείο της Εταιρείας (info@hasd.gr) ως συνημμένα αρχεία.

Μετά τον έλεγχο και εφόσον το άρθρο έχει γραφτεί σύμφωνα με τις οδηγίες που παρέχονται προς τους συγγραφείς, στέλνεται για ανεξάρτητη κρίση σε δύο αρμόδιους επιστημονικούς συμβούλους του περιο-

δικού (κριτές) χωρίς να φαίνονται τα ονόματα και η προέλευση της εργασίας.

Οι κρίσεις στη συνέχεια στέλνονται προς τους/τις συγγραφείς προκειμένου να γίνουν οι απαραίτητες τροποποιήσεις. Οι τελικές διορθώσεις που θα κάνει ο/η συγγραφέας σύμφωνα με τις υποδείξεις των κριτών, πρέπει να είναι υπογραμμισμένες ώστε να διευκολυνθεί ο σχετικός έλεγχος. Στη συνέχεια το άρθρο παίρνει σειρά δημοσιεύσεως.

ΒΑΣΙΚΕΣ ΟΔΗΓΙΕΣ

Η γραμματοσειρά του άρθρου πρέπει να είναι Times New Roman, το μέγεθος της γραμματοσειράς δεκατέσσερα (14) και η απόσταση των σειρών πρέπει να είναι 1,5.

Οι σελίδες των άρθρων πρέπει να είναι αριθμημένες διαδοχικά, ξεκινώντας από τη σελίδα τίτλου.

Οι συγγραφείς πρέπει να διατηρούν στο αρχείο τους αντίγραφα όλων των στοιχείων των εργασιών (εργαστηριακές εξετάσεις, απεικονιστικές εξετάσεις, ηλεκτροκαρδιογραφήματα, πορίσματα βιοψιών κ.τ.λ.) τις οποίες θα υποβάλλουν στον διευθυντή σύνταξης εφόσον τους ζητηθεί.

Κάθε άρθρο, ανάλογα με την κατηγορία στην οποία υπάγεται, πρέπει να ακολουθεί τους παρακάτω κανόνες και μορφή:

Πρώτη σελίδα – Σελίδα του τίτλου: Στη σελίδα αυτή αναγράφονται:

1) ο τίτλος του άρθρου, ο οποίος πρέπει να είναι κατά το δυνατόν σύντομος (όχι περισσότερες από 20 λέξεις) αλλά κατατοπιστικός,

2) το πρώτο όνομα, τα αρχικά του πατρικού (αν το επιθυμείτε), το επίθετο κάθε συγγραφέα και οι υψηλότεροι ακαδημαϊκοί τίτλοι (όχι ο τίτλος της θέσεως),

3) το όνομα των κλινικών, εργαστηρίων, τμημάτων ή και ιδρυμάτων στα οποία έγινε η εργασία,

4) το όνομα και η διεύθυνση του συγγραφέα που είναι υπεύθυνος για την αλληλογραφία, το e-mail και το τηλέφωνο επικοινωνίας του υπευθύνου σχετικά με την εργασία.

Δεύτερη σελίδα: Περιέχει την περίληψη στα Ελληνικά.

Οι ακόλουθες σελίδες περιέχουν το κείμενο της εργασίας με τον τύπο που ακολουθεί το περιοδικό.

Η τελευταία σελίδα περιέχει τον τίτλο και τα ονόματα του/των συγγραφέων, την Περίληψη στην αγγλική γλώσσα, και τους πρόσθετους Όρους ευρετηρίου στην ελληνική και αγγλική γλώσσα. Η περίληψη δεν πρέπει να υπερβαίνει τις 300 λέξεις και πρέπει να αναφέρει τον σκοπό της εργασίας, τη βασική μεθοδολογία (ασθενείς ή πειραματόζωα, παρατηρήσεις και αναλυτικές μεθόδους), τα κύρια ευρήματα (δώστε ειδικά στοιχεία και αναφέρετε αν τα ευρήματα είναι στατιστικώς σημαντικά) και τα κύρια συμπεράσματα. Τονίστε τις νέες και σημαντικές πλευρές της μελέτης ή των παρατηρήσεων. Χρησιμοποιήστε μόνο αποδεκτές συντμήσεις.

Κάτω από την περίληψη, σημειώστε και χαρακτηρίστε τρεις έως δέκα πρόσθετους όρους ευρετηρίου, οι οποίοι θα χρησιμοποιηθούν κατά την ετοιμασία του καταλόγου περιεχομένων. Χρησιμοποιήστε όρους οι οποίοι είναι γενικώς αποδεκτοί και χρησιμοποιούνται.

Πρωτότυπες εργασίες

Το κείμενο των κλινικών και πειραματικών εργασιών συνήθως διαιρείται σε τμήματα με τις εξής επικεφαλίδες: *Εισαγωγή, Υλικό –Μέθοδοι, Αποτελέσματα και Συζήτηση.* Μεγάλα άρθρα θα χρειαστούν οπωσδήποτε να κατατμηθούν σε τμήματα με καθορισμένο περιεχόμενο προκειμένου να παρουσιαστούν με σαφήνεια, ιδίως τα Αποτελέσματα και η Συζήτηση.

Εισαγωγή: Καθορίστε σαφώς τον σκοπό του άρθρου. Συνοψίστε τον αποχρώντα λόγο της συγγραφής της μελέτης ή της παρατήρησης. Δώστε τις αυστηρώς απαραίτητες βιβλιογραφίες και μην ανασκοπείτε το θέμα εκτενώς.

Υλικό – Μέθοδοι: Περιγράψτε με σαφήνεια τον τρόπο επιλογής του προς μελέτη υλικού (ασθενείς, πειραματόζωα και μάρτυρες). Περιγράψτε τις μεθόδους, τις συσκευές (όνομα και διεύθυνση του κατασκευαστή σε παρένθεση) και τις τεχνικές με αρκετές λεπτομέρειες, ώστε να επιτρέψετε σε άλλους συγγραφείς να αναπαράγουν τα αποτελέσματα. Δώστε βιβλιογραφία για καθιερωμένες μεθόδους, συμπεριλαμβανομένων και των στατιστικών μεθόδων που χρησιμοποιήθηκαν, καθώς και βιβλιογραφίες και βραχεία περιγραφή των μεθόδων, οι οποίες έχουν δημοσιευτεί αλλά δεν είναι γνωστές πολύ καλά. Περιγράψτε καινούριες ή ουσιαστικά τροποποιημένες μεθόδους, εξηγήστε τον λόγο που τις χρησιμοποιήσατε και κάντε μια εκτίμηση των περιορισμών τους.

Περιλάβετε τον αριθμό των παρατηρήσεων και, όταν κρίνετε απαραίτητο, τη στατιστική σημασία τους. Σε ειδικές περιπτώσεις είναι δυνατό να δοθούν λεπτομέρειες με τη μορφή πινάκων, ως παράρτημα, στο τέλος της εργασίας.

Αποτελέσματα: Παρουσιάστε τα αποτελέσματα σε μια λογική σειρά στο κείμενο, τους πίνακες και τα σχεδιαγράμματα. Μην επαναλαμβάνετε στο κείμενο τα στοιχεία που περιλαμβάνονται στους πίνακες ή τα σχεδιαγράμματα: τονίστε ή αναφερθείτε περιληπτικά μόνο στις σημαντικές παρατηρήσεις.

Συζήτηση: Τονίστε τις νέες και σημαντικές απόψεις που υποστηρίζονται από τη μελέτη και τα συμπεράσματα που προκύπτουν. Μην επαναλαμβάνετε λεπτομερώς τα δεδομένα που περιγράφονται στο κεφάλαιο των αποτελεσμάτων παρά μόνο τα κύρια ευρήματα κατά τη συζήτησή τους. Αναφερθείτε στη σημασία που έχουν τα ευρήματά σας, αξιολογώντας παράλληλα και τους περιορισμούς στην ερμηνεία τους και συσχετίστε τα με παρατηρήσεις που αναφέρονται σε άλλες ανάλογες μελέτες. Συνδέστε τα συμπεράσματα με τους στόχους της μελέτης, αλλά αποφύγετε να πάρετε θέση και να βγάλετε συμπεράσματα όταν δεν είναι τεκμηριωμένα και δεν υποστηρίζονται απόλυτα από τα δικά σας δεδομένα. Μην αναφέρετε συμπεράσματα άλλων συγγραφέων τα οποία όμως δεν προκύπτουν ως δεδομένα από την έρευνά σας.

Αποφεύγετε να δηλώνετε ή να διεκδικείτε προτεραιότητα για εργασία η οποία δεν έχει ακόμη ολοκληρωθεί. Κάντε νέες υποθέσεις, όταν δικαιολογούνται, αλλά χαρακτηρίστε τις έτσι σαφώς. Προτάσεις και εισηγήσεις, όταν κρίνεται απαραίτητο, μπορούν να περιληφθούν.

Ακολουθείστε το σύστημα Vancouver στην παράθεση των βιβλιογραφικών αναφορών (λεπτομερής περιγραφή παρατίθεται παρακάτω).

Περιορισμοί – μειονεκτήματα. Αναφερθείτε σε μειονεκτήματα που θεωρείτε ότι έχει η εργασία σας, π.χ., μικρός αριθμός ασθενών, ετερογενές υλικό, μικρή διάρκεια παρακολούθησης κ.ο.κ.

***Ευχαριστίες*:** Ευχαριστήστε μόνο τα πρόσωπα τα οποία έχουν ουσιαστική συμβολή στη μελέτη.

Λέξεις-κλειδιά: Γράψτε με προσοχή τις λέξεις-κλειδιά στην ελληνική και αγγλική γλώσσα ώστε να βοηθούν στην αναζήτηση σχετικών δημοσιεύσεων σε μια βάση δεδομένων (επισκεφθείτε την ηλεκτρονική βάση του περιοδικού http://www.hasd.gr/default.aspx?catid=277).

Ενδιαφέρουσες περιπτώσεις

Πρέπει να διακρίνονται στην ***περίληψη***, στην ***εισαγωγή***, στην ***περιγραφή της περίπτωσης*** (ιστορικό, συμπτώματα προσέλευσης, εργαστηριακός έλεγχος, πορεία νόσου, διαγνωστική λογική, έκβαση) και στη ***συζήτηση – συμπεράσματα***.

Ανασκοπήσεις

Ακολουθούν έναν επαγωγικό τρόπο παρουσίασης, με επιμέρους επικεφαλίδες, ώστε να διαβάζονται εύκολα. Πρέπει να περιλαμβάνουν πολλές βιβλιογραφικές παραπομπές (συνήθως άνω των πενήντα) και να καλύπτουν πλήρως το υπό πραγμάτευση θέμα.

ΒΙΒΛΙΟΓΡΑΦΙΑ

Παραδείγματα τρόπου γραφής των βιβλιογραφιών (κατά το σύστημα Vancouver):

Βιβλιογραφίες: Αριθμήστε τις βιβλιογραφικές παραπομπές διαδοχικά, με τη σειρά με την οποία αναφέρονται στο κείμενο. Χρησιμοποιήστε για τις βιβλιογραφίες στο κείμενο, στους πίνακες και στις λεζάντες, αραβικούς αριθμούς σε εκθέτες (1,2,3 κ.τ.λ.) μετά την τελεία της πρότασης (π.χ. …διαβητικής κετοξέωσης.[1]). Αν μια βιβλιογραφία επαναλαμβάνεται ισχύει ο αριθμός της πρώτης αναφοράς.

Οι τίτλοι των περιοδικών πρέπει να γράφονται κατά τον καθιερωμένο τρόπο για κάθε περιοδικό, σε συντομογραφία αν πρόκειται για λέξεις περισσότερες από μια (σύμφωνα με τον Index Medicus), π.χ., Diabet Med.

Προσπαθήστε να αποφύγετε τη χρησιμοποίηση περιλήψεων (abstracts) ως βιβλιογραφικών παραπομπών. «Αδημοσίευτες παρατηρήσεις» μπορεί να χρησιμοποιηθούν κατ' εξαίρεση εφόσον έχουν ανακοινωθεί ή αποτέλεσαν τμήμα βιβλίου. Η «προσωπική επικοινωνία» δεν πρέπει να χρησιμοποιείται ως βιβλιογραφία, αν και η παραπομπή σε γραπτή και όχι προφορική επικοινωνία μπορεί να αναφερθεί εμβόλιμα στο κείμενο (σε παρένθεση). Εργασίες οι οποίες έχουν γίνει δεκτές προς δημοσίευση, αλλά δεν δημοσιεύθηκαν ακόμη, μπορεί να αναφερθούν στη βιβλιογραφία. Στην περίπτωση αυτή σημειώστε το περιοδικό και τη φράση "in press" – «υπό δημοσίευση» (σε παρένθεση). Να μην αναφέρεται στις βιβλιογραφίες ο μήνας δημοσίευσης που συχνά παρέχεται στο pubmed. Αρκούν ο τόμος του περιοδικού, ο χρόνος και οι σελίδες του άρθρου. Η τελευταία σελίδα αναφέρεται συντετμημένα.

Άρθρα:

Τυπικό άρθρο περιοδικού (Γράψτε όλους τους συγγραφείς, εφόσον είναι έξι ή λιγότεροι· όταν είναι επτά ή περισσότεροι, αναφέρετε μόνο τους πρώτους τρεις και προσθέστε «et al» ή «και συν.» αν πρόκειται για ελληνική δημοσίευση):

You CH, Lee KY, Chey WY, Menguy R, et al. Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. Gastroenterology 1980; 79: 311-4.

Ενσωματωμένος συγγραφέας σε ομάδα εργασίας:

Royal Marsden Hospital Bone-Marrow Transplantation Team. Failure of syngeneic bone marrow graft without precon- ditioning in posthepatitis marrow aplasia. Lancet 1977; 2: 242-4.

Χωρίς συγγραφέα:

Anonymous. Coffee drinking and cancer of the pancreas (Editorial). Br Med J 1981; 283: 628.

Συμπληρωματικό τεύχος περιοδικού:

Mastri AR. Neuropathy of diabetic neurogenic bladder. Ann Intern Med 1980; 92: (Suppl. 2): 316-8.

Βιβλία και άλλες μονογραφίες:

Με έναν συγγραφέα:
Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974: 406.

Εκδότης, πρόεδρος μιας ομάδας εργασίας ως συγγραφέας:
Dausset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973: 12-8.

Κεφάλαιο σε βιβλίο:

Weistein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology; mechanisms of disease. Philadelphia: WB Saunders, 1974; 457-72.

Εργασία που περιέχεται σε τόμο πρακτικών:

DuPont B. Bone marrow transplantation in severe combined immunodeficiency with an unrelated MLC compatible donor. In: White HJ, Smith R, eds. Proceedings of the third

annual meeting of the International Society for Experimental Hematology. Houston: International Society for Experimental Hematology, 1974; 44-6.

Μονογραφή σε μια σειρά εκδόσεων:

Hunninghake GW, Gadek JE, Szapiel SV, et al. The human alveolar macrophage. In: Harris CC, ed. Cultured human cells and tissues in biomedical research. New York: Academic Press, 1980; 54-6 (Stoner GD, ed. Methods and perspectives in cell biology; vol 1).

Δημοσίευση επιτροπής:

Ranofsky AL. Surgical operations in short-stay hospitals: United States 1975. Hyattsville, Maryland: National Centre for Health Statistics, 1978; DHEW publication no. (PHS) 78-1785. (Vital and health statistics; series 13; no. 34).

Διδακτορική διατριβή:

Cairns RB. Infrared spectroscopic studies of solid oxygen. Berkeley, California: University of California, 1965. 156 pp. Dissertation.

Άλλα άρθρα

Άρθρο εφημερίδας:

Shaffer RA. Advances in chemistry are starting to unlock musteries of the brain: discoveries could help cure alcoholism and insomnia, explain mental illness. How the messengers work. Wall Street Journal 1977 Aug 12: 1 (col 1), 10 (col 1).

Άρθρο μη ιατρικού περιοδικού:

Roueché B. Annals of medicine: the Santa Claus culture. The New Yorker 1971 Sept 4: 66-81.

Οδηγίες για πίνακες, σχήματα και εικόνες

Πίνακες: Κάθε πίνακας πρέπει να είναι πλήρης, μαζί με τη λεζάντα του και τις υποσημειώσεις στην ελληνική γλώσσα. Η λεζάντα πρέπει να είναι στο πάνω μέρος του πίνακα και να προηγείται η λέξη «Πίνακας» με τον σχετικό αριθμό του (αραβικοί αριθμοί και όχι λατινικοί). Μην υποβάλλετε τους πίνακες ως φωτογραφίες. Σημειώστε σε κάθε στήλη μια βραχεία ή συντετμημένη επικεφαλίδα. Γράψτε τις επεξηγηματικές πληροφορίες ως υποσημείωση και όχι στον τίτλο. Εξηγήστε στις υποσημειώσεις όλες τις μη καθιερωμένες συντμήσεις που χρησιμοποιούνται σε κάθε πίνακα. Στις υποσημειώσεις χρησιμοποιήστε τα παρακάτω σύμβολα, με την εξής σειρά: *, **, +, ++, §, §§.

Εικόνες: Υποβάλλετε τις απαραίτητες εικόνες αριθμημένες (περιλαμβάνονται και τα σχήματα). Οι εικόνες πρέπει να αναφέρονται και στο κείμενο, ώστε να γνωρίζει ο υπεύθυνος σελιδοποίησης πού πρέπει να τοποθετηθούν. Τα γράμματα, οι αριθμοί και τα σύμβολα πρέπει να είναι σαφή, ομοιόμορφα και κατάλληλου μεγέθους έτσι ώστε, όταν σμικρυνθούν για τη δημοσίευση, να εξακολουθούν να παραμένουν ευανάγνωστα. Οι τίτλοι και οι λεπτομερείς επεξηγήσεις να γράφονται στις λεζάντες των εικόνων μετά την εικόνα (στο κάτω μέρος) και όχι πάνω στις ίδιες τις εικόνες, και πρέπει να είναι στην ελληνική γλώσσα εκτός από καθιερωμένους όρους σε σύντμηση, π.χ., HDL, TGF κ.τ.λ. Οι εικόνες πρέπει να υποβάλλονται ως χωριστά αρχεία εικόνων.

Μη χρησιμοποιείτε αυτούσια σχήματα ή εικόνες από ξένες δημοσιεύσεις γιατί τότε πρέπει να έχετε την άδεια του ξένου περιοδικού.

Αν υπάρχουν φωτογραφίες ατόμων, θα πρέπει είτε τα πρόσωπά τους να μην διακρίνονται ή να καλύπτονται με παχιά μαύρη επικάλυψη ή αν φαίνονται να συνοδεύονται από γραπτή άδεια των ασθενών για τη δημοσίευση των φωτογραφιών.

Αν μια φωτογραφία έχει δημοσιευθεί κάπου αλλού, σημειώστε στις ευχαριστίες την πηγή προέλευσης. Για όσες εικόνες απαιτείται άδεια από τον συγγραφέα/εκδότη πρέπει οι άδειες να επισυναφθούν στο άρθρο, εκτός και εάν είναι ελεύθερες για χρήση.

Λεζάντες των εικόνων: Οι λεζάντες των εικόνων μπαίνουν κάτω από την εικόνα (αντίθετα από ό,τι συμβαίνει στους πίνακες). Χρησιμοποιήστε για την αρίθμηση αραβικούς αριθμούς. Αν χρησιμοποιήσετε σύμβολα, βέλη, αριθμούς ή γράμματα για να χαρακτηρίσετε τμήματα των εικόνων, σημειώστε τα στο κάτω μέρος μετά την εικόνα και επεξηγήστε τα.

Η τήρηση των παραπάνω οδηγιών είναι απαραίτητη προϋπόθεση για τη δημοσίευση της εργασίας.

Πνευματικά δικαιώματα

Οι εργασίες που δημοσιεύονται στα *Ελληνικά Διαβητολογικά Χρονικά* αποτελούν πνευματική ιδιοκτησία του συγγραφέα και του περιοδικού. Η δημοσίευση μιας εργασίας δεν συνεπάγεται αποδοχή των απόψεων των συγγραφέων από μέρους του περιοδικού.

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1st Joint International Meeting

"Diabetes Mellitus. From Basic Research To The Day-To-Day Clinical Practice"

Co-organized by the Department of Internal Medicine IV, University of Tübingen and the Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, along with the Hellenic Association for the Study & Education of Diabetes Mellitus

18-20 May 2018, Thessaloniki Greece

Hellenic Diabetological Chronicles 31, 2: 63-65, 2018

Diabetes Mellitus in ancient Greek medical writings Aretaeus of Cappadocia, "On the Causes and Symptoms of Acute and Chronic Diseases 2.2"*

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The very first attestation of the disease of *diabetes mellitus*, yet not of the exact term *diabetes*, is believed to be traced in one of the oldest extant papyri, namely, the 'Ebers Papyrus', dating to circa 1550 BC and discovered in 1872 at Luxor by Georg Ebers. This medical document comprises a discussion of a certain "disease involving polyuria, no physical pain, but melting down of the flesh", also reports that this disease is accompanied by an overall physical fatigue and records prescriptive medicine for treating polyuria. Medical prescriptions of drugs also appear in other ancient papyri (Hearst papyrus, c. 2000 BC; Brugsch papyrus, c. 1350-1200 BC).

In the treatises of the Hippocratic corpus there is no record of the disease. The work by Soranus of Ephesus (1st/2nd c. AD) entitled *On Acute and Chronic Diseases*, which has been preserved only via the Latin edited translation by the physician Caelius Aurelianus (5th c. AD), quotes, in the chapter *De hydrope* (*On hydrops*), what the physician Apollonius of Memphis in Egypt (fl. 250/200 BC) believed of the disease. Apollonious is credited with distinguishing two forms of dropsy, namely, one comprising fluid retention and one where massive fluid discharge through urine occurs. This latter form of dropsy, is identified by modern scholars with *diabetes*. Apollonius associates the disease with the kidneys, as do all subsequent physicians, and recommends, among other therapeutic treatments, such measures as phlebotomy and dehydration. Be that as it may, in the text attributed to him there is no mention of the term *diabetes*; as Caelius Aurelianus notes:

> '*Apollonius of Memphis declares that one form of dropsy is marked by retention <of fluid, and another form as an inability to retain>, so that whatever the patient drinks is immediately discharged as if it is passed through a tube. And, in agreement with the majority of physicians, he asserts that this certain type of thirst that leads to retention appears in three distinct forms.'*

The term *diabetes* was presumably coined by the physician Demetrius of Apamea, Bithynia (late 3rd c. BC – early 1st c. BC).

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* Honorary lecture during the opening ceremony

This view, which is the most likely to be true, is also reported by Caelius Aurelianus:

> *'but Demetrius of Apamea more properly distinguishes from dropsy the disease in which everything that is drunk is immediately discharged as urine and he (Demetrius) calls this disease diabetes, which we shall further discuss in a separate section'*

[unfortunately this special chapter on diabetes, foreshadowed here, has not been preserved].

The next occurrence of the term *diabetes* is in the work of the physician Aretaeus of Cappadocia, who flourished in all probability in Rome (mid. 1st c. AD). He was, according to the model of the Hippocratic physician, an adherent of the clinical practice and the thorough observation. One of the most widely known texts of Aretaeus is the second chapter of the second book of his work entitled *On the Causes and Symptoms of Acute and Chronic Diseases*, where he focuses on *diabetes* (*On Diabetes*). Aretaeus has been credited with introducing the term *diabetes* on the basis of the following text he wrote:

> *'The disease appears to me to have got the name of* diabetes *(which in Greek signifies a siphon) because the fluid (urine) does not remain in the body, but uses the human body as a ladder whereby to find an exit'.*

However, the above phrasing does not imply that Aretaeus actually introduced the term but rather that the term was already current in his era. It is obvious that the Cappadocian physician does not suggest a term for the disease but merely explains why, in his view, the term *diabetes* was coined for the disease by one of his predecessors. This view is corroborated by the passage quoted above, which attributes the coinage of the term for the disease to Demetrius of Apamea. *Diabetes* was presumably linked to Aretaeus owing to the fact that the most thorough clinical description of the disease in antiquity originates in him, while no earlier description has been preserved. The description of *diabetes* according to Aretaeus is as follows:

> *'Diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine. Its cause is of a cold and humid nature, as in dropsy. The course is the common one, namely, the kidneys and bladder; for the patients never stop making water, but the flow is incessant, as if from the opening of aqueducts. The nature of the disease, then, is chronic, and it takes a long period to form; but the patient is short-lived, if the constitution of the disease be completely established; for the melting is rapid, the death speedy. Moreover, life is disgusting and painful; thirst, unquenchable; excessive drinking, which, however, is disproportionate to the large quantity of urine, for more urine is passed; and one cannot stop them either from drinking or making water. Or if for a time they abstain from drinking, their mouth becomes parched and their body dry; the viscera seem as if scorched up; they are affected with nausea, restlessness, and a burning thirst; and at no distant term they expire. Thirst, as if scorched up with fire. But by what method could they be restrained from making water? Or how can shame become more potent than pain? And even if they were to restrain themselves for a short time, they become swelled in the loins, scrotum, and hips; and when they give vent, they discharge the collected urine, and the swellings subside, for the overflow passes to the bladder. If the disease be fully established, it is strongly marked; but if it be merely coming on, the patients have the mouth parched, saliva white, frothy, as if from thirst (for the thirst is not yet confirmed), weight in the hypochondriac region. A sensation of heat or of cold from the stomach to the bladder is, as it were, the advent of the approaching disease; they now make a little more water than usual, and there is thirst, but not yet great.*
> *But if it increase still more, the heat is small indeed, but pungent, and seated in the intestines; the abdomen shrivelled, veins protuberant, general emaciation, when the quantity of urine and the thirst have already increased; and when, at the same time, the sensation appears at the extremity of the member, the patients immediately make water. Hence, the disease appears to me to have got the name of diabetes, as if from the Greek word διαβήτης (which signifies a siphon), because the fluid does not remain in the body, but uses the man's body as a ladder (διαβάθρη), whereby to leave it. They stand out for a certain time, though not very long, for they pass urine with pain, and the emaciation is dreadful; nor does any great portion of the drink get into the system, and many parts of the flesh pass out along with the urine.*

The cause of it may be, that some one of the acute diseases may have terminated in this; and during the crisis the diseases may have left some malignity lurking in the part. It is not improbable, also, that something pernicious, derived from the other diseases which attack the bladder and kidneys, may sometimes prove the cause of this affection. But if any one is bitten by the dipsas, the affection induced by the wound is of this nature; for the reptile, the dipsas, if it bite one, kindles up an unquenchable thirst. For they drink copiously, not as a remedy for the thirst, but so as to produce repletion of the bowels by the insatiable desire of drink. But if one be pained by the distension of the bowels and feel uncomfortable, and abstain from drink for a little, he again drinks copiously from thirst, and thus the evils alternate; for the thirst and the drink conspire together. Others do not pass urine, nor is there any relief from what is drank. Wherefore, what from insatiable thirst, an overflow of liquids, and distension of the belly, the patients have suddenly burst'.

Also, in the corresponding therapeutic chapter, namely, in *On the Cure of Acute and Chronic Diseases* 2.2, and more specifically in the first section of the chapter, Aretaeus sums up, so to speak, the pathology of *diabetes* before expanding on the cure.

In nearly all prominent physicians coming after Aretaeus, *diabetes* is mentioned either in passim or in a disctinct chapter of their work; however, nothing important is added to the inferences and the description offered by the Cappadocian physician (they all unfailingly follow Aretaeus and Galen). Nevertheless, these medical authors also inform us about the alternative terms for the disease; these terms are 'dropsy in the chamber-pot'; 'diarrhoea in urine'; 'unquenchable thirst sickness'; and leiouria (polyuria).

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Antihypertensive drugs and their combination in Diabetes Mellitus

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Nowadays, a huge section of worldwide population suffers from Diabetes mellitus (DM) and this proportion is expected to increase in coming years. More than half, that have Diabetes mellitus, have also, Arterial hypertension (HTN). DM raises the cardiovascular risk and is the main cause of chronic kidney failure final stage and blindness in adults. The co-existence of DM and HTN multiplies and accelerates the risk of micro- and macro- vascular complications. Consequently, the need for optimal control of DM and simultaneously of HTN, is imperative. The data of plenty clinical trials revealed the benefit of the excellent regulation of Blood Pressure (BP) in individuals with DM. Therefore the American Diabetes Association, the European Society of Hypertension, the European Society of Cardiology and the American Heart Association determined the target values of ideal BP. BP targets have to be lower than <140/90 mmHg, and values approaching 130/80 mmHg should be recommended. However, evidence in favour of even lower systolic values, i.e. <130 mmHg, is limited and is definitively against a reduction to <120 mmHg. According to the results of recent studies, the target of BP remains a difficult goal, since the percentage of the successful regulation of BP is very low.

The therapeutic approach of HTN in individuals with DM includes lifestyle modifications and pharmacological interventions. Potentially, the administration of any antihypertensive drug is acceptable, as long as the therapy is personalized for the patients and their co-morbidities. Certainly the medication necessary comprise a blocker of the renin-angiotensin system, videlicet an inhibitor of angiotensin converting enzyme (ACE-I) or an antagonist of type-1 angiotensin II (ARB).

The ideal antihypertensive agents for patients with DM, should not interfere with metabolism, prevent the onset of hypoglycaemia, do not cause orthostatic hypotension, nor aggravate dyslipidemia, peripheral vascular disease, coronary artery disease or sexual dysfunction.

According to recent studies in individuals with DM, the BP target is achieved by the use of 2 to 3 antihypertensive drugs on average. This fact highlights the need to use potent combinations of antihypertensive drugs. In addition, the use of antihypertensive drugs

combination reduces the BP more directly and effectively. Furthermore, the drug combination, due to the synergy of the active substances by different mechanisms of action, reduces the adverse effects of drugs, while lower dosages are required. Moreover, the combination of drugs in ready, fixed doses, leads to better patient compliance in treatment, while reducing the cost of treatment.

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Diabetic Ketoacidosis

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Diabetic ketoacidosis (DKA) is an acute and life-threatening metabolic complication mostly attributed to type 1 diabetes mellitus and in some cases to type 2 diabetes mellitus, as well as to gestational diabetes. DKA was first described in 1886 and, until the introduction of insulin therapy in the 1920s, it was almost universally fatal. DKA occurs in 4.6-8.0 per 1000 people with diabetes annually. DKA is the first event in T1DM at a rate of 21.1%, more often in children under 5 years old. Mortality rate in DKA is at 4%.

DKA is characterized by a complete lack of insulin and hypersecretion of competitive hormones leading to increased release of glucose by the liver (a process that is normally suppressed by insulin) from glycogen via glycogenolysis and also through gluconeogenesis. High glucose levels spill over into the urine, taking water and solutes (such as sodium and potassium) along with it in a process known as osmotic diuresis. This causes polyuria, dehydration and polydipsia. The absence of insulin also provokes release of free fatty acids from adipose tissue (lipolysis), which are converted through a process called beta oxidation, again in the liver, into ketone bodies (acetoacetate and β-hydroxybutyrate acids). The ketone bodies, however, have a low pKa and therefore turn the blood acidic (metabolic acidosis).

No causative factor is present at a rate of 22-25%. Triggers may include infection, not taking insulin correctly, myocardial infarction and certain medications such as steroids. The symptoms of an episode of diabetic ketoacidosis usually evolve over a period of about 24 hours. Predominant symptoms are nausea and vomiting, pronounced thirst, excessive urine production and abdominal pain. In severe DKA, breathing becomes rapid and of a deep, gasping character, called "Kussmaul breathing". The abdomen may be tender to the point that a serious abdominal condition may be suspected, such as acute pancreatitis, appendicitis or gastrointestinal perforation. In severe DKA, there may be confusion or a marked decrease in alertness, including coma.

On physical examination there is usually clinical evidence of dehydration, such as a dry mouth and decreased skin turgor as well as rapid heart rate and low blood pressure. Often, a "ketotic" odor is present, which is often described as "fruity". Small children with DKA are relatively prone to brain swelling, also called cerebral ede-

ma, which may cause headache, coma, loss of the pupillary light reflex, and can progress to death. It occurs in about 1 out of 100 children with DKA and more rarely occurs in adults.

DKA is typically diagnosed when testing finds high blood sugar, low blood pH, and ketoacids in either the blood or urine. The average adult with DKA has a total body water shortage of about 6 liters (or 100 mL/kg), in addition to substantial shortages in sodium, potassium, chloride, phosphate, magnesium and calcium. Glucose levels usually exceed 13.8 mmol/L or 250 mg/dL. The hallmark of DKA is a high-anion- gap metabolic acidosis. Glucose serum levels are not always extremely elevated. In addition to the above, blood samples are usually taken to measure urea and creatinine (measures of kidney function, which may be impaired in DKA as a result of dehydration) and electrolytes. Furthermore, markers of infection (complete blood count, C-reactive protein) and acute pancreatitis (amylase and lipase) may be measured. Given the need to exclude infection, chest radiography and urinalysis are usually performed.

The American Diabetes Association categorizes DKA in adults into one of three stages of severity:

Mild: blood pH mildly decreased to between 7.25 and 7.30 (normal 7.35-7.45); serum bicarbonate decreased to 15-18 mmol/l (normal above 20); the person is alert

Moderate: pH 7.00-7.25, bicarbonate 10-15, mild drowsiness may be present

Severe: pH below 7.00, bicarbonate below 10, stupor or coma may occur

DKA must be differentiated from hyperosmolar hyperglycemic state and other severe cases such as lactic acidosis, alcoholic ketoacidosis, starvation, poisoning from salicylics, methanol, ethylenoglycol and paraldehyde.

The cornerstones of treatment are rehydration, IV insulin and potassium supplementation. The primary treatment of DKA is with intravenous fluids. A special but unusual consideration is cardiogenic shock, where the blood pressure is decreased not due to dehydration but due to inability of the heart to pump blood through the blood vessels. This situation requires ICU admission.

Insulin regular can be infused intravenously after the potassium level is known to be higher than 3.3 mmol/l; if the level is any lower, administering insulin could lead to a dangerously low potassium level. Intravenous insulin administration should continue until acidosis has been reversed. Usually, potassium chloride is needed to prevent the development of low blood levels of potassium which increases the risk of dangerous irregularities in the heart rate. In those with severely low blood pH (pH < 6,9), sodium bicarbonate may be given; however, its use is of unclear benefit and typically not recommended. Throughout treatment blood sugar and potassium levels should be regularly checked. Antibiotics may be required in those with an underlying infection. Thromboprophylaxis with low molecular weight heparin is imperative.

Resolution of DKA is defined as general improvement in the symptoms, such as the ability to tolerate oral nutrition and fluids, normalization of blood acidity (pH>7.3) and absence of ketones in blood (<1 mmol/l) or urine. Once this has been achieved, insulin may be switched to the usual subcutaneously administrered regimen, one hour after which the intravenous administration can be discontinued.

Attacks of DKA can be prevented in those known to have diabetes to an extent by adherence to "sick day rules"; these are clear-cut instructions to person on how to treat themselves when unwell. Instructions include advice on how much extra insulin to take when sugar levels appear uncontrolled, an easily digestible diet rich in salt and carbohydrates, means to suppress fever and treat infection and recommendations when to call for medical help. People with diabetes can monitor their own ketone levels when unwell and seek help if they are elevated.

There has been a documented increasing trend to hospital admissions due to DKA. It is attributed to changes in case definition, new medications that might increase the risk for DKA (SGLT-2 inhibitors) and higher admission rates because of lower thresholds for hospitalization (i.e., admission of persons with less serious disease). Mortality rates have been declining over the past few years, but remain close to 4%. The decrease in mortality is brought about from a combination of lower incidence of DKA, earlier diagnosis and improved treatment in specialized diabetes clinics.

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New predictive Biomarkers and novel therapeutic target in Diabetic Nephropathy

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Diabetic nephropathy (DN) is the most important cause of end-stage renal disease (ESRD) and a main factor of diabetes (DM) – related morbidity and mortality. However, its pathophysiological underlying mechanisms remain unclear. Podocyte injury and/or apoptosis is recognized as a hallmark of the renal disease process characterized by failure of the filtration barrier. Hyperglycaemia-mediated podocyte apoptosis and podocyte depletion occurs in animal and human models of both type 1 and type 2 DM. Podocytopenia is present at the early stages of both type 1 and type 2 DM. The coexistence of glomerular basement membrane (GBM) expansion and hyperglycaemia-induced podocyte injury and enhanced apoptosis leads to a marked increase in membranepermeability, thus predisposing to the development of diabetic albuminuria. The diagnosis of DN is traditionally based on the presence of micro-albuminuria (MA). MA has been used indicating the progression of chronic kidney disease (CKD), but it could also cause renal damage in patients with CKD. Further, there is accumulating evidence that proteinuria is an independent risk factor for cardiovascular disease (CVD) as well. Several recent studies have reported these observations suggesting the link between proteinuria, CKD and CVD. However, MA is not an adequate predictor of DN in young or in patients without albuminuria and additional biomarkers of glomerular and tubular injury have been proposed to denude structural lesions of early renal disfunction before the presence of MA. New predictive biomarkers would expose patients at the initial stages of DN, those who will progress to the ESRD and provide preventive and therapeutic interventions of irreversible longterm complications. Biomarkers of glomerular injury, tubular injury, inflammation and oxidative stress precede albuminuria in DN patients, also overlapping each other classification. Glomerular biomarkers include immunoglobulin G (IgG 4, IgG 2 isoforms), ceruloplasmin, collagen type IV (col-IV), laminin, glycosaminoglycans (GAGs), lipocalin-type prostaglandin D synthase (L-PGDS), fibronectin, podocytes-podocalyxin, and vascular endothelial growth factor (VEGF). Podocalyxin and VEGF are essentially considered as podocyte biomarkers. Laminin and col-IV are components of GBM, although the later is also a component of mesangial matrix.

Newer approaches include urinary microRNAs which are short noncoding mRNAs that regulate gene expression and urine proteomics, highlighting a possible role for epigenetic factors in the development of the disease.

Tubular biomarkers have shown that tubular dysfunction can be present early in DN and are early predictors of DN compared to microalbuminuria and other glomerular biomarkers. This category includes neutrophil gelatinase-associated lipocalin (NGAL), α-1-microglobulin, kidney injury molecule 1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), cystatin C, and liver-type fatty acid-binding protein (L-FABP).

Biomarkers of inflammation such as TNF-α, IL-1β, IL-6 and IL-18, are involved in the onset and progression with predictive roles in DN. Other biomarkers of inflammation, which are also glomerular markers, include interferon gamma-induced protein (IP-10), monocyte chemoattractant protein 1 (MCP-1), granulocyte colony-stimulating factor (G-CSF), eotaxins, RANTES (regulated on activation, normal T cell expressed and secreted) or Chemokine ligand-5 (CCL-5), and orosomucoid.

Biomarkers of oxidative stress are urinary 8-oxo-7,8-dihydro-2-deoxyguanosine (8oHdG), lipid peroxides, malondialdehyde (MDA) and superoxide dismutase (SOD). The marker of 8oHdG is produced secondary to oxidative DNA damage, and appears in the urine without being metabolized. Biomarkers of fibrosis are col-IV, fibronectin, transforming growth factor β (TGF-β1), matrix metalloproteinase - 2 (MMP-2), tissue inhibitor of metalloprotease-1 (TIMP-1) with pathological accumulation in the glomerulus and tubulointerstitial space significantly associated with renal outcomes in diabetic patients. New therapeutic aspects have shown protective affects against renal fibrosis in a mouse model of type 2 diabetes, including reduction in glomerular col-IV.

Graphical Abstract

Matrix Gelatinases (MMP-2 and -9), TGF-β1, VEGF-A, TIMP-1 and -2, FGF-23, Col-IV in Atherosclerosis – Inflammation – Fibrosis of Diabetic Nephropathy and disease process with Albuminuria: Progress and Challenges.

DN represents an example of the link between progressive glomerulosclerosis and MMP expression. In vitro studies high glucose levels was associated with an increased expression of matrix molecules, whereas the activity of MMPs, namely MMP-2 and -9, was decreased in mesangial cells. In general, down-regulation of MMPs' expression has been associated with the progression of renal dysfunction to CKD in non-inflammatory diseases such as DN. There is a link between intrarenal dysregulation of MMP activity and the development of DN. Pro-inflammatory cytokines have also been associated with DN via theregulation of MMP expression. In details, cytokines such as IL-1, IL-6 and TNF-α stimulate MMP production, whereas factors such as TGF-β, corticoid hormone and insulin-like growth factor (IGF) down-regulate MMP synthesis. A role for glucose and advanced glycation end-products (AGEs) in the regulation of MMP expression have also been demonstrated. Altered MMP expression or activation contributes to DN, and especially to the onset of this characteristic renal hypertrophy, as abnormal extracellular matrix (ECM) deposition is the hallmark of DN. Apart from the direct effect of MMPs on ECM turnover, MMPs may also release and activate several growth factors that have been associated with renal hypertrophy, tubular

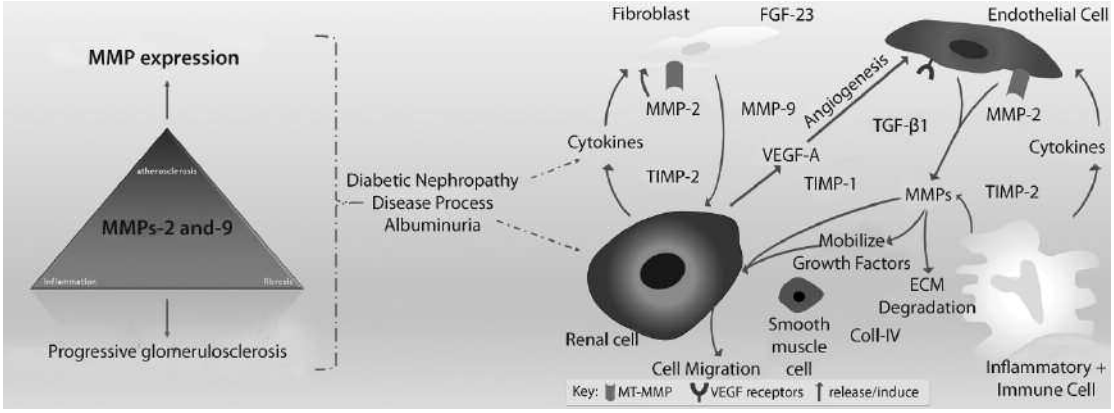

Figure 1

cell proliferation and renal scarring and fibrosis.

Both MMP-2 and -9 are the main enzymes that degrade col-IV, the major collagenous component of the ECM and the architectural structure of BM and GBM. BM is the part of the ECM that is associated with the vascular endothelium. MMP-2 over-expression in transgenic renal proximal tubular epithelium is sufficient to reflect the characteristic pathologic changes of CKD. Data from rodent models suggest a link between MMP-2 dysregulation and DN, but there are also controversial results. In such rodent models of DN the expression and proteolytic activity of MMP-2 in renal tissues was reduced and the activity of TIMP-2 was increased. In contrast, MMP-2 activity was elevated 3.8-6 fold in protein extracts of human diabetic kidney tissue samples. The increased circulating MMP-2 levels in diabetic patients may be explained by the confounding effects of diabetes treatment. For example, insulin can induce MMP-2 activity in rat glomerular mesangial cells (Figure 1).

Dysregulated activity of various growth factors and cytokines may contribute to the development of renal abnormalities in DN. Such growth factors involved in DN are TGF-β, VEGF, connective tissue growth factor (CTGF), IGF, epidermal growth factor (EGF) and platelet derived growth factor (PDGF); TGF-β and VEGF are better known and more widely investigated. TGF-β inhibits MMPs and activates TIMPs. TGF-β also up-regulates integrins, the cell surface receptors for ECM, enhancing cellular ability to interact with specific matrix proteins.

VEGF, a key angiogenic factor, influencing the proliferation of endothelial cells, plays a pivotal role in vascular integrity and pathological angiogenesis and it has been implicated in DN. TGF-β through the signalling pathway of intracellular proteins that transduce extracellular signals, namely small mother against decapentaplegic (SMADs) also regulates VEGF.

New predictive biomarkers uncovering the initial stages of DN, even before MA occurs, would provide an opportunity for preventive and therapeutic interventions preventing or delaying the onset of irreversible long-term complications and improving outcomes, results in a reduction of the severe cardio-renal morbidity and mortality progress in diabetic kidney disease patients.

The future of Preventive Medicine development and drug discovery depends on the selection and validation of rapid, reliable, and quantitative assays of disease biomarkers.

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Anemia and Diabetes Mellitus

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Diabetes Mellitus (DM) is considered a major public health problem. Its frequency is increasing worldwide, particularly in the Western world and estimations suggest that 1 in 3 adults in the US is likely to suffer from diabetes in 2050. About 25% of diabetic patients is assumed to have anemia. The risk in diabetics to develop anemia is estimated to be 2-3 times higher then the general population, when comparing patients with similar glomerular filtration rate (eGFR) and iron levels. It has been observed that prolonged duration of DM may increase the incidence of anemia in diabetics[1,2]. The etiology of anemia in diabetics is a complex, multi-factorial and often unrecognized issue (table)[3,4].

Table. Possible causes of anemia in diabetics.

1	Chronic blood loss
2	Iron deficiency
3	B_{12} or follate deficiency
4	Relative erythropoietin deficiency (EPO)
5	EPO resistance associated with chronic infection or inflammation
6	Autonomic neuropathy
7	Converting enzyme inhibitors (ACEis) or angiotensin II receptor inhibitors (ARBs)
8	Nephrotic syndrome
9	Increased catabolism of HIF complex, associated with hyperglycemia
10	Decreased red blood cell survival time
11	Hypothyroidism

In diabetics with an eGFR less than 60 ml/min, anemia is observed in 29%, while in diabetics with an eGFR higher than 60 ml/min only in 9%[5]. Hepcidin, a peptide hormone released by the liver, seems to be the key regulator of iron homeostasis and could be possibly used as an index of anemia, iron status and inflammation, as well as a therapeutic target. It inhibits ferroportin, a protein responsible for the intestinal absorption of iron, leading to a consequent reduction of iron's absorption. Additionally, hepcidin increases the difficulty for iron to be released from its storages in

macrophages and hepatocytes (leading to functional iron deficiency). In CKD −due to decreased clearance of hepcidin through kidneys− its levels are increased and this partly explains the iron deficiency in diabetic patients with CKD[6]. In addition the effect of antidiabetic drugs on circulating hepcidin has not been explored so far; it is only established that metformin treatment is not associated with reductions in hepcidin, but hypocaloric diet could be involved in it[7].

Glycosylated hemoglobin (HbA_1C), which is an irreversible nonenzymatic process that depends on the glucose concentration in red blood cells, is used as an important diagnostic index to assess glycemia and has low intraindividual variability. The association between anemia and concentrations of HbA_1C has received limited attention. HbA_1C constitutes the measurement of the non-enzymatic glycosylation of the beta-chain of the Hb molecule, whose levels are affected by a variety of genetic, hematologic and disease-related factors. The most important factors are coexistence of hemoglobinopathies, coexistence of various anemias and disorders related to acceleration of the regeneration rate of the red blood cells. Every situation that contributes to increased erythrocyte turnover (anemia of chronic disease, hemolytic anemias, anemia after acute blood loss), results in falsely low HbA_1C[8].

In contrast, iron deficiency anemia may lead to a false increase in HbA1C, causing changes to the shape of Hb molecule promoting glycation of the terminal valine or by lowering the erythrocyte turn over, thus allowing more time for glycation of Hb[9,10]. The haematologic status should therefore always be taken into account for a correct interpretation of the HbA1C result. According to the guidelines of the National Academy of Clinical Biochemistry, it is recommended for all samples of HbA1C to be remeasured by the laboratory, when values lower than the reference interval (<4%) are detected. Should they be confirmed, the clinician is adviced to check for a variation of the patients Hb (hemoglobinopathy) or an indication of increased red cell destruction[11,12]. It should be strongly noted that HbA1C should only be used for glycemia assessment in the absence of anemia. The recurrent measurement of Hb, iron, and HbA1C is vital to correctly assess the glycemia status in order to avoid misclassification between diabetes and prediabetes. People with anemia who appear on the border of the diagnostic threshold of diabetes may require the use of another diagnostic method, such as fructosamine or glycated albumin (excluding situations where protein metabolism is amended)[12]. Furthermore, red blood cell transfusion can complicate the interpretation of HbA1c values in diabetic patients, because it introduces haemoglobin molecules exposed to glucose concentrations that may have been different from the glucose concentrations in the diabetic transfusion recipient[13]. The ADA recommendation is to measure HbA1c in all hospitalized diabetic patients who have not had an HbA1c measurement taken within the previous 60 days, and the American Joint Commission has adopted this recommendation as a standard for inpatient diabetes care[14].

Treatment of anemia in DM lacks clear targets and specific therapy is not well defined. Recent studies on the correction of anemia in diabetic patients (ACORD, CREATE, CHOIR, TREAT), in contrast to the clinical practice so far, showed that therapeutic interventions concerning anemia with EPO administration or intravenous iron, should be attempted at an early stage of DM and not only at the CKD phase[15-18]. However, both erythropoietin analogs (epoetin-A and darbepoetin) and iron are not without side effects. At high doses, EPO is implicated in hypertension, thrombotic and cardiovascular events and in inducing the growth of various neoplasms. Hypertension occurs 2-16 weeks after starting treatment and does not depend on the Ht increase, but on the increase of intracellular calcium, which both inhibit the vasodilating action of nitric oxide (NO) and cause direct vasoconstriction in arterioles. EPO effect on hemostasis is mediated by a quantitative increase and consequent improvement of platelet function, in addition to a reduction in proteins C and S[19]. Moreover, iron administered in a high dosage may cause hemosiderosis and increase the sensitivity of the body to infections[20]. Target hemoglobin concentration is now lower and a trial of iron therapy alone is advised before decision for EPO administration, which is recommended in diabetic anemic patients, only when CKD coexists, in order to achieve Hb levels between 10,0-12,0 g/dl, but not higher. Of course, the benefit from the early treatment of anemia in diabetics should be considered versus the cost of the treatment for the patient and the health system[21].

Up until now it is well established that HbA1c levels can be affected by conditions such as anemia. There are very few population-based studies, with small sample size examining the differences in the prevalence of diabetes and prediabetes according to categories of anemia versus normal Hb. Additional studies with larger numbers of participants with anemia would be helpful in examining the impact of anemia and its correction on measurements of HbA_1C.

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Glycemic control in hospitalized patients

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In the hospital setting, hyperglycemia is considered any blood glucose (BG) above 140 mg/dl. Patients with type 1 or type 2 diabetes mellitus (DM) are frequently admitted to a hospital, usually for treatment of conditions other than the diabetes. As the prevalence of diabetes and the prevalence of other diseases rises with increasing age, it is more likely that an older person admitted to a hospital will have DM. However, 12% of hospitalized patients have hyperglycemia without known prior history of diabetes. In that case an HbA1c should be performed and a value ≥6.5% suggests that diabetes preceded hospitalization, though an HbA1c value <6.5% suggests stress induced hyperglycemia.

A lot of retrospective and observational data indicate that poor inpatient glycemic control is associated with worse outcomes and increased morbidity and mortality in patients with or without diabetes. However, there is no evidence from randomized trials to demonstrate that tight glycemic control (BG target level of 80-110 mg/dl) in inpatients can improve outcomes. In contrast, patients who experience hypoglycemia during a hospitalization tend to have a longer length of stay. In the hospital setting, both hyperglycemia and hypoglycemia are associated with adverse outcomes, including death. Therefore, inpatient goals should include the prevention of both them.

According to current recommendations of American Diabetes Association, BG levels should be regulated at a starting threshold of 180 mg/dl. A target glucose between 140 mg/dl and 180 mg/dl appears safe and acceptable for the majority of general medicine and surgery patients in non-ICU and ICU settings. Tight glucose control may be appropriate for selected patients, as long as this can be achieved without significant hypoglycemia.

Insulin is the best way to control hyperglycemia in the inpatient setting specially in the critically ill patient. Continuous intravenous infusion is the preferred regimen for critically ill patients in the ICU and scheduled subcutaneous administration with a basal -bolus regimen with correctional insulin is the preferred method for achieving glycemic control in the non-ICU setting. Sole use of sliding scale insulin in the inpatient hospital setting is strongly discouraged. The use of oral antidiabetic agents is not recommended because the lack

of safety and efficacy studies in the inpatient setting. However, increasing evidence indicates that treatment with DPP4 inhibitors, alone or in combination with basal insulin, is safe and effective in general medicine and surgery with mild to moderate hyperglycemia. For effective and safe in-hospital BG control, a guidance protocol must be developed for each center.

The main goals in patients with diabetes needing hospitalization are to minimize metabolic disturbance, prevent acute adverse glycemic events and return the patient to a stable glycemic state as quickly as possible. There should be an effective transition to outpatient care in order to prevent acute complications and readmission. These goals are not easy to be achieved as on the one hand the stress of the acute illness raises BG but on the other hand, gastrointestinal symptoms and anorexia that are often present at hospitalized patients have negative impact on glycemic control.

The HbA1c level on admission is critical for post-hospitalization treatment. Although insulin is the most appropriate regimen during hospitalization, patients with acceptable glycemic control can continue to receive their previous treatment. There should be a structured discharge plan for each patient, especially those newly in insulin, to prevent readmission.

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Nutrition before and during gestation in pre-existing diabetes and in gestational diabetes

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The prevalence of diabetes in pregnancy has been increasing worldwide. The majority is gestational diabetes mellitus (GDM) with the remainder primarily preexisting type 1 diabetes and type 2 diabetes. Pregestational uncontrolled diabetes has a tremendous impact on the health of the fetus associated with congenital anomalies which may affect several organ systems. After organogenesis, maternal, fetal and neonatal effects include miscarriage, preeclampsia, macrosomia, hypoglycemia, respiratory distress syndrome and stillbirth. Also, diabetes in pregnancy may increase the risk of obesity and type 2 diabetes in offspring later in life. Moreover, Women with GDM are at high risk of developing type 2 diabetes after pregnancy.

Medical Nutrition Therapy (MNT) is the cornerstone of diabetes management in pregnancy. It is the only therapy for 40%-58% of women with GDM. The MNT provides an individualized nutrition plan to help control blood glucose and to promote appropriate gestational weight gain. During pregnancy, the nutritional goal is to provide adequate calorie intake and nutrients with guidance from the Dietary Reference Intakes (DRI) in order to support thedeveloping baby, while limiting episo des of hyperglycemia and avoiding hypoglycemic events and the production of ketones (especially for women with type 1 diabetes). Specific dietary recommendations are poorly studied during pregnancy and no data exists to support one dietary approach over another.

Last but not least, preconception dietary counseling is equally important and provides an opportunity to inform patients of the risk of diabetes in pregnancy and to use that time when the patient is most motivated to initiate lifestyle changes that will improve both pregnancy outcome and the patient's long-term health status.

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How the brain controls peripheral metabolism in humans

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Over the last years, the human brain has been recognized as an insulin sensitive organ. Of note, only a limited number of brain areas respond to the peptide hormone. These include prefrontal areas that are crucial for the inhibitory control of behavior as well as higher visual areas where food stimuli are processed by the brain. One important function of insulin in those regions appears to be the modulation of eating behavior. Insulin also acts in the hippocampus, an important area for memory and cognition. Just as in animals, the human hypothalamus responds to insulin. This brain area is the center for the homeostatic control of the rest of the body and contributes to the modulation of peripheral insulin sensitivity as well as glucose fluxes throughout the body.

Similar to the periphery, the brain can become insulin resistant. This condition is associated with abdominal obesity, increasing age, elevated levels of circulating saturated free fatty acids as well as a number of genetic variants that predispose for obesity.

Research from our department and others demonstrated that brain insulin action improves peripheral insulin sensitivity in humans. Brain-derived signals reach peripheral tissues mainly via the autonomic nervous system.

Using hyperinsulinemic-euglycemic clamps, we recently demonstrated that insulin administration to the human brain improves peripheral insulin sensitivity by suppressing endogenous glucose productionand stimulating glucose uptake into tissue. This mechanism is, however, only detectable in lean and healthy but not in obese volunteers (who are brain insulin resistant).

The modulation of peripheral insulin sensitivity by brain insulin action appears to be strongly dependent on the prandial state. In the postprandial situation (where brain insulin action occurs in physiology), brain-derived outflows improve peripheral insulin sensitivity to suppress endogenous glucose production and stimulate glucose uptake into tissue. In contrast, under fasting conditions, the brain responds to insulin and parasympathetic outflows are activated, however, this does not translate into beneficial metabolic effects.

Thus, overcoming brain insulin resistance will likely result in metabolic benefits like improved glucose tolerance and reduced dia-

betes risk. Besides these metabolic effects, restored brain insulin action will have positive results also directly in the brain where it could shift eating behavior towards a healthy diet, improve cognitive function and even reduce the risk for neurodegenerative processes. Strategies to improve brain insulin sensitivity that are currently investigated include weight loss as well as the applications of various types of antidiabetic drugs.

Thus, the brain as the metabolic mastermind is an excellent novel target to prevent and treat metabolic diseases and complications thereof.

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The role of triglycerides in the pathogenesis of microvascular complications of diabetes mellitus

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Microvascular complications of diabetes mellitus (DM) represent a major public health problem. Approximately 34%-40% of patients with DM have chronic kidney disease (albuminuria or impaired kidney function). Moreover, 3.3% of adults in US have diabetic nephropathy whereas in subjects > 65 years-old, 10.7% has diabetic nephropathy. In addition, 44% of patients undergoing dialysis in the US have DM. Importantly, patients with diabetic nephropathy have higher all-cause mortality than patients with coronary heart disease. Regarding diabetic retinopathy, it affects 27%-40% of patients with DM and is leading cause of blindness in working-aged adults. Even though the incidence of diabetic retinopathy has declined in the last decades, its prevalence increased and is expected to rise further as a result of the increasing incidence of type 2 DM and the longer life expectancy of patients with DM. Diabetic neuropathy is the most early complication of DM and the leading cause of non-traumatic amputation in high-income countries. Autonomic diabetic neuropathy is also associated with increased cardiovascular risk.

Emerging data suggest that elevated triglycerides are implicated in the pathogenesis of microvascular complications of DM. Several observational studies in patients with both type 1 and type 2 DM suggested that elevated triglyceride levels are associated with increased risk for development of albuminuria and for decline in renal function. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (n = 988 patients with type 1 DM) and in the Early Treatment Diabetic Retinopathy Study (n = 3.711 patients with type 2 DM), the severity of retinopathy was positively associated with triglyceride levels. In contrast, triglyceride levels do not appear to predict the progression of retinopathy in patients with type 1 DM. Moreover, several observational studies in both patients with type 1 and type 2 DM suggested that elevated triglyceride levels are associated with increased risk for development of peripheral and autonomic neuropathy.

It also appears that the reduction of triglyceride levels with fibrates prevents or delays the progression of microvascular complications of DM. In the Diabetes Atherosclerosis Intervention Study (n = 314 patients with type 2 DM), treatment with fenofibrate for 38 months reduced the worsening of albumin excretion and reduced the

incidence of new-onset microalbuminuria.In the *Fenofibrate* Intervention and Event Lowering in Diabetes (FIELD) trial (n = 9.795 patients with type 2 DM), patients who received fenofibrate experienced an increase in serum creatinine levels by 0.11 mg/dl more than patients treated with placebo but the decline of glomerular filtration rate during the study was slower in patients treated with fenofibrate (by 0.8 ml/min/1.73m^2 annually compared with placebo) during a follow-up of 5 years. Fenofibrate also reduced urine albumin excretion by 14% more than placebo. In the Action to Control Cardiovascular Risk in Type 2 Diabetes (*ACCORD*)trial (n = 5.518 patients with type 2 DM), patients who received fenofibrate combined with simvastatin experienced an increase in serum creatinine levels by 0.06 mg/dl more than patients treated with simvastatin monotherapy during a follow-up of 4.7 years. On the other hand, fenofibrate reduced the incidence of both new-onset microalbuminuria and new-onset macroalbuminuria by 10%. Regarding the effects of fibrates on diabetic retinopathy, in the FIELD trial, treatment with fenofibrate for 5 years reduced the need for laser photocoagulation by 31% (p = 0.002) compared with placebo. Fenofibrate also reduced the risk of progression of retinopathy by 79% (p = 0.004). It was estimated that 17 patients with retinopathy had to be treated with fenofibrate for 5 years to prevent one laser treatment. However, fenofibrate had no effect on the development of retinopathy in patients without retinopathy at baseline. Moreover, fenofibrate did not prevent the deterioration of visual acuity. In the ACCORD Eye study (n = 2.856 patients with type 2 DM), treatment with fenofibrate for 4 years reduced the rate of progression of retinopathy by 40% (p=0.006) compared with placebo. However, fenofibrate did not affect the occurrence of moderate vision loss. Fenofibrate is currently licensed in some countries for the management of diabetic retinopathy. Finally, regarding the effects of fibrates on diabetic neuropathy, in the Fremantle Diabetes Study (1,237 patients with type 2 DM), the use of fenofibrate was independently associated with 70% lower risk for prevalent peripheral neuropathy. Moreover, in the prospective cohort of the same study (531 patients with type 2 DM followed-up for 5 years), treatment with fenofibrate reduced the risk of incident peripheral neuropathy by 48%. In the FIELD trial, fenofibrate reduced the risk of first amputation by 36% and the risk of minor amputation without known large-vessel disease by 47%. However, fenofibrate had no effect on the incidence of major amputations.

It should be mentioned that the beneficial effects of fibrates on the microvascular complications of DM are not an indisputable proof that triglycerides are implicated in the pathogenesis of these complications. Indeed, fibrate increase high density lipoprotein cholesterol (HDL-C) levels and also exert antiinflammatory and antioxidant effects. These actions might also play a role in the prevention and treatment of microvascular complications of DM. Indeed, the effects of fibrates on microvascular complications appeared to be independent of changes in the lipid profile. Moreover, these benefits were apparent within 8 months of initiation of fenofibrate treatment, suggesting that other mechanisms than lipid-lowering might be implicated.

More limited data suggest that omega-3 fatty acids, which also reduce triglyceride levels, might also prevent or delay the progression of microvascular complications of DM. In a recent study in 262 patients with type 2 DM, treatment with omega-3 fatty acids for 1 year prevented the increase in albuminuria. In another recent study in 344 patients with type 2 DMI, treatment with omega-3 fatty acids for a median of 1.4 years reduced albuminuria and prevented the decline in renal function. Regarding the effects of omega-3 fatty acids on diabetic retinopathy, in an early study, administration of omega-3 fatty acids to streptozotocin-induced diabetic rats did not affect pericyte loss and increased the formation of acellular, occluded capillaries in the retina. In contrast, in more recent animal studies, treatment with omega-3 fatty acids preserved retinal function. However, there are no studies that evaluated the effects of omega-3 fatty acids on diabetic retinopathy in humans. Finally, regarding the effects of omega-3 fatty acids on diabetic neuropathy, in an early study in patients with type 2 DM, treatment with eicosapentaenoic acid for 48 weeks improved clinical symptoms (coldness, numbness) and the vibration perception threshold sense of the lower extremities. In a pilot study in 40 patients with type 1 DM, treatment with omega-3 fatty acids for 1 year increased corneal nerve fiber length but did not affect sensory function or nerve conduction. In another study in 24 patients with type 2 DM, treatment with

omega-3 fatty acids for 6 months improved autonomic neuropathy. However, these preliminary data do not necessarily mean that triglycerides are implicated in the pathogenesis of microvascular complications of DM, since omega-3 fatty acids also appear to exert antiinflammatory and antioxidant effects, which might also play a role in the amelioration of these complications.

In conclusion, epidemiological data suggest that triglycerides might be implicated in the pathogenesis of all microvascular complications of DM. Clinical studies also suggest that reduction of triglyceride levels with either fibrates or omega-3 fatty acids might prevent or improve these complications. However, other mechanisms might also be implicated in these beneficial effects of fibrates and omega-3 fatty acids. More importantly, the effects of reduction of triglyceride levels on the macrovascular complications of DM are unclear. Therefore, lowering triglycerides is not currently recommended as a part of the prevention or management of the microvascular complications of DM. Treatment with fibrates or omega-3 fatty acids is recommended only in patients who have non-HDL-C levels > 100 mg/dl despite achieving low-density lipoprotein cholesterol targets with a potent statin.

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HbA1c for screening and diagnosis of Diabetes Mellitus – applications and future perspectives

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Diabetes mellitus affects almost one in 10 individuals in Germany. So far, little is known about the diabetes prevalence in maximum care hospitals. We assessed the diabetes prevalence, proportion of undiagnosed cases, the effectiveness of diabetes screening in a university hospital, the consequences for hospital stay and acquired complications.

Over a 4 week period we determined HbA1c from 3.733 adult patients which were hospitalized at the university hospital of Tuebingen and had an available blood sample. Diabetes diagnosis was defined as HbA1c≥6.5% and/or previously documented diabetes diagnosis, prediabetes was defined as HbA1c≥5.7% and <6.5% without history of previous diabetes.

The study revealed that 23.68% of the patients had prediabetes and 22.15% had diabetes with a high variation between the specialized departments (range 5%-43%). The rate of unknown diabetes was 3.7%, the number needed to screen was 17 in patients older than 50 years. Patients with diabetes had a prolonged hospital stay compared to the mean length of stay for their diagnosis related group (diabetes: 1.47±0.24 days; no diabetes: 0.18±0.13 days, p=0.0133). The prevalence of hospital acquired complications was higher in diabetic patients (diabetes: 197 of 630; no diabetes: 447 of 2.459, p<0.0001).

In conclusion, every fourth patient in the university hospital had diabetes and every second had either prediabetes or diabetes. It is also worthwhile to screen for unknown diabetes in patients over the age of 50. The high prevalence and negative consequences of diabetes require screening and intensified specialized diabetes treatment in hospitals. Extension of the screening program to comorbidities and complications (e.g. nephropathy) and modification of the screening parameters may further increase the clinical value of this multidisciplinary effort.

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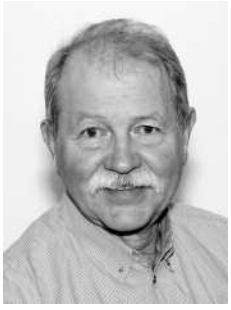
Discrepancies of blood glucose and HbA1c in diabetic patients – How to proceed in individual cases

Erwin Schleicher



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Diabetes mellitus is defined as an heterogenous metabolic disorder with chronic hyperglycemia as leading symptom. Apart from clinical symptoms which may be unspecific, particularly in type 2 diabetes, both blood glucose and HbA1c values are used to confirm the diagnosis. Furthermore, both laboratory parameters are widely used to assess metabolic control. However, although both parameter measure different substances i.e. glucose indicating acute blood glucose concentration while HbA1c is an indirect measure for long-term hyperglycemia, both parameter is interpreted in a similar way. This may result in misdiagnosed or undiagnosed diabetes. As an example, in a young woman diabetes was diagnosed on the basis of an elevated HbA1c of 7.6% and treated with insulin. After one year the elevated values could be explained by a revisited history of the patient indicating a reduced erythrocyte life-span due to splenectomy after an accident. In case of laboratory values with no corresponding clinic the clinician may use both parameters to support the diagnosis. If there are discrepancies between glucose and HbA1c values an interference of the analytical measurement including preanalytical influences, may be present or HbA1c is influenced by the individual per se.

Particularly two conditions influence the HbA1c value:

1. reduced or increased erythrocyte life-span due to anemia (untreated as well as treated which may lead to enhanced erythropoiesis) or intravasal hemolysis either endogenous or induced by drugs or recent blood loss e.g. by accident or blood donation
2. patholocicalhemoglobins which may influence the erythrocyte life-span and possibly also the measurement dependent on the method used

None of these conditions influences or interferes with the blood glucose concentration/measurement.

While there is no laboratory parameter at present for the determination of erythrocyte life-span increased erythropoiesis may be estimated from an increased reticulocyte count. In case of pathological hemoglobins or other interference factors the determination of fructosamine may help to estimate the glycemia of the patient.

But also more general parameters influence the HbA1c value. These include age (increase), bad metabolic control (increase), eth-

nicity e.g. afro-americans (increase) etc.

In case of pregnancy, liver cirrhosis or severe diabetic nephropathy/hemodialysis the HbA1c values are not valid. While plasma glucose is not influenced by the above mentioned factors, preanalytical factors are important for unbiased determination and interpretation of glucose values.

Most important factors are the inadequate handling of the glucose sample (special tubes are needed to prevent glycolysis) and the nutritional state of the patient (fasting or postprandial).

Taken together, HbA1c and glucose measurement complement each other and should be used knowing the advantages and disadvantages of either parameter. The knowledge should also include the different predictive value of both parameters e.g. HbA1c correlates with diabetic microvascular complication, particularly diabetic retinopathy, while a pathological oGTT may predict an increased risk for cardiovascular complications.

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A novel combination of basal insulin and GLP-1 analog

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The progressive nature of type 2 diabetes necessitates that treatment is intensified as the disease advances. Several studies have shown that basal insulin and glucagon-like peptide-1 receptoragonists (GLP-1RAs) can be used in combination to successfully improve glycemic control and this combination is increasingly being considered as an alternative to intensification with prandial insulin.

Insulin degludec/liraglutide (IDegLira) is the first fixed-ratio combination of a basal insulin and a GLP-1RA in a single formulation. IDegLira offers an efficacious combination therapy (mean end-of-trial HbA1c was 6.4%-6.9% across the five completed Phase 3 trials), which was well-tolerated in clinical trials. The complementary modes of action resulted in a low rate of hypoglycemia and no weight gain ininsulin-treated patients. As a once-daily injection with effects on both fasting and post prandial hyperglycemia, IDegLira has the potential to help many patients reach glycemic target (60%-81% of patients achieved HbA1c <7% in clinical trials).

The complex pathophysiology of type 2 diabetes is characterized by declining β-cell function resulting in reduced insulin secretion in response to glucose, hyper secretion of glucagon from pancreatic α-cells and insulin resistance in the muscle and liver. This favors a strategic approach involving combinationtherapy that can address the full spectrum of underlying abnormalities and maximize the chance of treatment success. Metformin is recommendedas first-line therapy in most patients with type 2 diabetes, and it is recommended that an additional therapy be added if a patient is not at target after 3-6 months treatment. Incretin and insulin therapies are both efficacious blood glucose lowering therapies, but with different mechanisms of action. GLP-1RAs increase insulin secretion by β-cells and decrease glucagon secretion by α-cells, both in a glucose-dependent manner.

Depending on their duration of action, they can decrease both fasting plasma glucose (FPG) and postprandial glucose (PPG), with longeracting GLP-1RAs having a greater effect on FPG and shorter acting products having a greater effect on PPG. GLP-1RAs also reduce satiety, delay gastric emptying, can reduce body weight and areassociated with a low risk of hypoglycemia. However, GLP-1RAsmay not lead to sufficient insulin secretion from β-cells to achieve

the desired glycemic control. Basal insulin therapy increases circulating insulin in a non-glucose-dependent manner and has been associated with improved β-cell function. Basal insulin has a role in glucose regulation in the liver and peripheral tissues, and modulates hepatic glucose production. Basal insulin is very effective at lowering HbA1c and FPG, but has less of an effect on PPG.

Insulin is associated with an increase in body weight (due in part to increased appetite and food intake) and a risk of hypoglycemia. Therefore, the two mechanisms of action may complement each other, with the glucose-dependent effect of GLP-1RAs on pancreatic islet function counterbalancing the risk of hypoglycemia observed with increasing doses of insulin. By reducing hunger and food intake, GLP-1RAs can decrease the weight gain associated with insulin. The individual effects of basal insulin and GLP-1RAs suggest a theoretical rationale for combination therapy with clinical benefits to be expected.

As described above, the beneficial effects of combining incretin and insulin therapies have now been well documented. When titrated as per the clinical trials and guidelines, IDegLira offers a treatment that is likely to be less complex than adding-multiple prandial insulin injections to basal insulin plus OADs, perhaps making therapy adherence less difficult for patients.The end-of-trial HbA1c was particularly impressive in the IDegLira arms of DUAL I–V, with high numbers of patients reaching glycemic target after 26 weeks of treatment, and many patients not requiring the maximum dose in order to do so. In the context of existing therapies, IDegLira provides a novel treatment option that could enable more patients to reach glycemic target, thereby avoiding or delaying future diabetic complications.

It is important to consider where this therapy will fit in the pathway of diabetes care. When patients remain above target on OADs, treatment algorithms recommend therapy intensification. However, the initiation of injectable therapy after oral agents can be problematic and therefore delayed, as is often observed for insulin and therefore potentially IDegLira, too. The combination of an effective basal insulin and an effective GLP-1RA in a single co-formulation for once-daily injection,without compromising the properties of either, provides a simple, user-friendly approach to therapy intensification for a broad spectrum of patients. In our study we investigated the clinical outcomes in a real-world population with long standing, poorly controlled type 2 diabetes mellitus (T2DM) after switching from oral antidiabetic drugs(OADs), GLP-1 RAs or/and insulin to IDegLira [a combination of insulin degludec (IDeg) and liraglutide (Lira)].We observed that mean HbA_{1c} reduced with IDegLira versus previous regimens significantly (8.9%±1.6% vs 7.3%±0.7%, $p < 0.001$). There was a mean decrease in weight of 3 kg with IDegLira (97.4%±18.4 kg vs 94.4%±18.4 Kg, $p < 0.001$) during the three months follow up. There was a decline in mean systolic (135.6±19.4 mmHg vs 130.7±16.4 mmHg, $p < 0.05$), also. Mean dose of IDegLira was 35.9±13.8 dose steps/24h. There were no episodes of severe hypoglycemia during treatment with IDegLira. In conclusion from our study, switching to IDegLira, mostly from regimens using insulin together with oral antidiabetic drugs (OADs) in a real-world population of patients with type 2 diabetes, resulted in improved glycemic control along with weight loss and lower systolic blood pressure. The safety profile with IDegLira was consistent with previous findings.

Furthermore, IDegLira was well tolerated: the rate of hypoglycemia with IDegLira was lower than that with insulin degludec alone and the rate of gastrointestinal side effects was lower than with liraglutide alone in all studies mentioned above.

To summarize, Insulin degludec/liraglutide (IDegLira) is the first fixed-ratio combination of a basal insulin (insulin degludec) and a glucagon-like peptide-1 receptor agonists (liraglutide) available in a single once-daily injection. It is an attractive and effective combination for patients and there are clear benefits associated with use of a fixed ratio single injection in terms of glycemic control, body weight and hypoglycemia. IDegLira associated with a low incidence of side effects for many of our patients with type 2 diabetes, also.

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Diagnosis and Treatment of Angiopathy in Diabetes

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The prevalence of diabetes is increasing world-wide. Diabetes and also the stage of prediabetes are well-known risk factors for microvascular and macrovascular diseases. Subjects with diabetes, but without manifest cardiovascular disease (CVD) have the same risk of CVD mortality as subjects with myocardial infarction. A 60-year old man/women with diabetes but without manifest CVD has ~6/7 years of life lost, compared to a subject without diabetes. These numbers increase to ~12/14 years if a patient with diabetes has established CVD. In respect to CVD myocardial infarction and stroke are the most widely known diseases that are being screened for in diabetes. However, peripheral artery disease may also place subjects with diabetes in a risk category, similar to the one with established CVD. If so, then peripheral artery disease may already represent a state of secondary prevention of CVD and CVD-mortality. There is much information in the literature supporting this hypothesis. For example in epidemiological studies the presence of peripheral artery disease poses even a somewhat higher risk of myocardial infarction (MI), stroke and CVD-mortality than history of MI.

Many patients with diabetes already have peripheral artery disease, prior to the manifestation of CVD. Thus, the question is; which diagnostic criteria should be used to screen for peripheral artery disease in a clinical setting? In this respect the ankle-brachial index is a well-established tool. If the results are suggestive of manifest peripheral artery disease Doppler ultrasound examination of the leg is the next step to evaluate the severity and locations if stenosis. In some cases MR-angiography or CT-angiography is required to precisely locate and evaluate the stenosis. Among the interventive procedures endovascular strategies, open surgery or hybrid therapies should be considered.

Pharmacological treatment of patients with peripheral artery disease with or without diabetes include antiplatelet agents such as aspirin or clopidgrel. Even the treatment with rivaroxaban seems promising (COMPASS trial). Statin therapy has been shown to cause reductions in all-cause mortality and CV events.

Furthermore, carotic artery plaques or carotic artery stenosis also pose subjects with diabetes at high risk of stroke. In this respect the diagnosis of carotic artery plaques or stenosis should be imple-

mented in the diagnostic setting of patients with long-standing diabetes or diabetes + metabolic syndrome. The diagnostic procedures include Duplex ultrasound as first-line imaging. CT-angiography and MR-angiography help evaluating severity and extent of extracranial carotid stenosis if necessary.

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Crosstalk between fatty liver and pancreatic adiopocytes accentuates local inflammation and impairs insulin secretion

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Obesity-linked ectopic fat accumulation increases the risk of the development of type-2 diabetes mellitus. While liver steatosis (NAFLD) is well accepted as an adverse factor, pancreatic fat accumulation is controversially discussed. This study aims to characterize the pancreatic fat compartment and its role in islet function.

The immuno histological analysis of human pancreatic resections suggests that differentiated adipocytes, identified by oil red and adiponectin staining, infiltrated the exocrine tissue and occasionally even the endocrine tissue. Islets surrounded by adipocytes displayed normal architecture and endocrine cell distribution as determined by insulin, glucagon and somatostatin immunostaining. The proximity of adipocytes to islets correlated with an increased number of CD68-positive cells within the islets.

In order to examine pancreatic fat cells in more detail primary preadipocytes were isolated and differentiated *in vitro* to adipocytes. Both, preadipocytes and adipocytes, were exposed to palmitate and fetuin-A to mimic a cross-talk between fatty pancreas and fatty liver. Under control culture condition, cytokine production was low. The exogenously addition of palmitate and fetuin-A to the culture medium stimulated IL6, CXCL8 and CCL2 expression and secretion of primary pancreatic preadipocytes as well as of differentiated adipocytes. This stimulation was TLR4 dependent. When the effect of pancreatic fat cell on islet function was examined in a co-culture system, cytokine production of preadipocytes was further increased.

In addition, in isolated human islets from organ donors, fetuin-A and palmitate increased IL-1β, IL6 and CXCL8 mRNA levels. The up-regulation of IL-1β occurred exclusively in macrophages which infiltrated the islets. As expected, palmitate stimulated apoptotic islet cell death, whereas Fetuin-A did not alter beta-cell death. Fetuin-Areduced glucose-induced insulin secretion (GIIS). The effect of fetuin-A was abrogated by an inhibitor (SP600125) of the stress kinase JNK. Fetuin-A inhibition of GIIS was also counteracted by an increase of extracellular Ca2+, but, interestingly, persisted in the presence of TLR4 inhibition.

These results suggest that in obese humans increased plasma levels of palmitate, i.e. long chain saturated fatty acids, and fetuin-A, released from fatty liver, stimulate cytokine production of pancreatic fat cells which augments local inflammation. An additional fetuin-A-mediated metabolic crosstalk of fatty liver with islets directly affects GIIS.

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Metabolically Healthy Obese and Metabolically Obese-Normal Weight individuals

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Obesity, defined as a BMI over 30 kg/m^2, is well known to be closely associated with insulin resistance and related cardiometabolic risk factors, eventually leading to type 2 diabetes, cardiovascular disease, and possibly to malignancies[1]. However, a subset of obese patients do not display this traditional cardiometabolic risk profile. These are known as the 'metabolically healthy obese' (MHO). Conversely, although normal weight individuals with a BMI in the range 20-25 kg/m^2 seem to have the lowest all-cause mortality[2], a subset of them shoulder an increased risk of developing metabolic and cardiovascular diseases ('metabolically unhealthy normal weight'-MUNW). Metabolic health definitions are based on the absence of insulin resistance, type 2 diabetes, dyslipidemia, hypertension and systemic inflammation, but greatly vary in terms of the number and cutoffs of these risk factors between different researchers and different studies[3]. Due to this inconsistency, there is a high degree of variability in the reported prevalence of the MHO and MUNW phenotypes. Most studies however suggest that in any given moment about 1 out of 4 obese and about 1 out of 10 normal weight individuals demonstrate the MHO and MUNW phenotypes, respectively[4-6].

While the existence (and the relatively high prevalence) of MHO and MUNW individuals in cross-sectional studies is not questioned, there is an ongoing discussion whether these individuals retain their status in the long-term, i.e. whether the MHO display about the same and MUNW a worse metabolic and cardiovascular risk compared to 'metabolically healthy' normal weight (MHNW) humans. In this respect, large meta-analyses of longitudinal studies (many of them with more than 10 years duration) have shown that both, the incidence of cardiovascular events and all-cause and cardiovascular mortality of MHO individuals are somehow higher compared to MHNW individuals, but much lower compared to 'metabolically unhealthy' obese (MUO) individuals. Of particular note, MUNW individuals display cardiovascular morbidity and mortality rates almost as high (or even higher in some analyses) as MUO[7-9]. MHO and MUNW status seem to confer a similar risk of developing diabetes in the future, which is higher than the respective risk of MHNW but clearly lower than the risk of MUO[10,11]. These data imply that MHO and MUNW may constitute only tem-

porary states. Nevertheless, large observational studies have suggested that about 2/3 of MHO and MUNW subjects retain their status (and the respective cardiometabolic risk) after a follow-up of 6-10 years[12,13]. About one-third of MHO lose their 'metabolic health' being rendered to MUO. Interestingly, at follow-up, this population shows a 4-5 times higher prevalence of diabetes and cardiovascular events compared to those who retain their MHO status. In contrast, one-third of MUNW gain their 'metabolic health' and display similar to MHNW prevalence of diabetes and cardiovascular disease at follow-up[12,13].

The precise mechanisms leading to MHO and MUNW phenotypes are not known. Nevertheless, elegant studies in transgenic animal models and humans suggest that the status of metabolic health is associated with a specific body fat distribution, i.e. low visceral fat mass, low liver fat content and high amounts of subcutaneous fat, a favourable adipokines and cytokines profile (mainly high adiponectin levels), and a low grade of adipose tissue and systemic inflammation[4,14,15]. In this setting, hepatokines, i.e. several proteins that are exclusively or predominantly secreted from a fatty liver and directly affect glucose and lipid metabolism, may play a particularly important role[16]. The best studied hepatokine, fetuin-A, for instance, is an endogenous inhibitor or insulin receptor, thus inducing insulin resistance, and has been shown to induce inflammation by interacting with free fatty acids and thereby activating toll-like receptors-4[16-18]. In an effort to clarify whether the same mechanisms contribute equally to the pathogenesis of the MHO and MUNW phenotypes, we recently analyzed data from 981 subjects at increased cardiometabolic risk, because of overweight or obesity, a family history of type 2 diabetes, a personal history of gestational diabetes, or of having prediabetes during an OGTT. We identified fatty liver, visceral obesity, low percentage of subcutaneous leg fat (gluteofemoral) mass, high insulin resistance, low insulin secretion capacity and low cardiorespiratory fitness on a cycle ergometer as being determinants of the 'metabolically unhealthy' status both in normal weight and obese subjects[6]. However, the relative contribution of fatty liver, visceral obesity and insulin resistance is greater in obese than in normal-weight individuals, whereas the relative contribution of low percentage of subcutaneous leg fat mass is greater in normal weight individuals (that is, gluteofemoralf at may be a major determinant of the MUNW phenotype)[6]. Gluteofemoral fat was shown to release higher, compared to subcutaneous abdominal adipose tissue, amounts of the insulin-sensitizing lipokine palmitoleate[19,20]. This may constitute a possible mechanism partly explaining the protective effect of this fat depot.

Genetics certainly play a role in the pathogenesis of the MHO and MUNW phenotypes, but their relative importance remains elusive. Association studies in large cohorts suggest that the effect maybe exerted by affecting body fat distribution. The Frayling groupfor instance, using data from about 200.000 individuals from the UK Biobank and 5 other studies, showed that 11 single nucleotide polymorphisms (SNPs) are associated with a 'favourable adiposity', i.e. a higher BMI and higher body fat mass, but lower waist-to-hip ratio and lower prevalence of type 2 diabetes, hypertension and heart disease[21]. Conversely, certain other SNPs and genetic loci were reported to be related to high insulin resistance and high prevalence of diabetes and hypertension, but a low BMI and lower subcutaneous (particularly gluteofemoral) adipose mass, i.e. to a MUNW-like phenotype[21-23].

The knowledge of the pathophysiology may be relevant for making proper treatment decisions. For MUNW, there are not consensus guidelines or clinical practice recommendations. Obviously, a healthy lifestyle should be always recommended, and pharmacological treatment of hyperglycemia, hyper- or dyslipidemia and hypertension should be added whenever this is considered to be necessary. Nevertheless, if low subcutaneous leg fat plays indeed a key role in the pathogenesis of MUNW, thiazolidinediones (TZDs) may represent a particularly attractive approach, because of their ability to promote adipose tissue differentiation while simultaneously improving hyperglycemia. However and in addition to their known side-effects, TZDs did not prove to be effective in treating lipodystrophies (a kind of 'extreme MUNW'), and this applies even in the cases resulting from peroxisome-proliferator–activated receptor γ mutations[24].

With regard to MHO, the main question is whether the general guidelines for obesity should apply also in individuals 'metabolically healthy'. Only few studies have tested the effectiveness of a

lifestyle intervention, the first-choice treatment of obesity according to the guidelines, in MHO individuals[25-29]. A reduction in visceral and liver fat and an improvement in insulin sensitivity were observed. However, the magnitude of the response was mostly rather limited and generally smaller than the response of the MHO to the same lifestyle intervention. Although all these studies refer to short-time lifestyle interventions (up to 9 months) and therefore had no 'hard' endpoints (diabetes, cardiovascular events), their results suggest that structured, time-consuming and costly lifestyle intervention programs may not be justified in MHO individuals. Considering however, as mentioned before, that the long-term risk of losing the 'metabolic health' status is about 30%, it is reasonable to advise these people to follow a healthy lifestyle and remain under continuous medical supervision.

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Non-Alcoholic Fatty Liver disease. Who and how to treat to reduce Cardiometabolic Risk

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The prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing world-wide and 25 percent of the general adult population in the world is affected by NAFLD. In Western countries 3 to 10 percent of all children and about 70 percent of obese children are considered to have NAFLD. This increase in the prevalence of NAFLD is accompanying the increasing prevalence of the non-communicable diseases type 2 diabetes, cardiovascular disease, obesity- and type 2 diabetes-associated cancer and advanced liver diseases, such as hepatic cirrhosis and hepatic cancer.

Subjects with NAFLD often are obese and/or have impaired glucose and lipid metabolism with characteristics of metabolically unhealthy normal weight or obesity, insulin resistance, prediabetes and/or type 2 diabetes. Therefore, it remains unclear to what extent specifically the prevention and treatment of NAFLD may reduce morbidity and mortality in these subjects. Furthermore, NAFLD is a very heterogeneous disease, which can be categorized histologically into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) and which has a somewhat different risk of progression to advanced stages of liver disease. In addition, the increased cardiometabolic risk in NAFLD varies among these different stages of NAFLD and is very high in the presence of advanced stages of NAFLD, such as NASH with moderate to advanced fibrosis.

Lifestyle intervention is the primary therapeutic approach in NAFLD. However, while a mean weight loss of ~5% considerably reduces liver fat content, more than 10% of weight loss is thought to effectively reduce hepatic inflammation. Finally, even such a large weight loss appears not to considerably improve hepatic fibrosis in most patients with NAFLD. Thus, in addition to the lifestyle intervention, pharmacological intervention becomes necessary in many patients with advanced stages of NAFLD. However, results from pharmacological clinical trials in patients with NAFLD revealed that each agent tested has a broad spectrum of effects in respect to their anti-inflammatory, anti-fibrotic and cardiometabolic efficacy. Thus, a tailored therapeutic approach based on precise phenotyping of the hepatic and cardiometabolic risk is necessary to provide personalized treatment to our patients with NAFLD.

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Focus on empagliflozin's efficacy and EMPAREG-OUTCOME study's data

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Type 2 diabetes is a major risk factor for cardiovascular disease[1,2] and the coexistence of cardiovascular disease and type 2 diabetes increases the risk of death[3]. Although a modest cardiovascular benefit may be observed after a prolonged follow up, evidence that glucose lowering reduces the rates of cardiovascular events and more important death has not been convincingly shown[4-6]. Moreover, the use of specific glucose lowering drugs as well as intensive glucose lowering may be associated with adverse cardiovascular outcomes[7,8]. Therefore, the cardiovascular safety benefits of glucose-lowering agents should be established[9].

Inhibitors of sodium-glucose cotransporter 2 reduce rates of hyperglycemia in patients with type 2 diabetes by decreasing renal glucose absorption, thereby increasing urinary glucose excretion[10]. Empagliflozin is a selective inhibitor of sodium glucose cotransporter 2[11] that has been approved for type 2 diabetes[12]. The drug reduces glycated hemoglobin levels in patients with type 2 diabetes, including those with stage 2 or 3a chronic kidney disease[13-20], given as either monotherapy or as add on therapy. Moreover, it is reported to reduce blood pressure without increases in heart rate[13-20] and has favorable effects on markers of arterial stiffness and vascular resistance[21], albuminuria[20] and plasma urate[13-19]. Empagliflozin is also associated with weight loss and reduction of visceral adiposity[22]. The most common side effects of empagliflozin are urinary tract infection and genital infection[12].

In the EMPA-REG OUTCOME trial, the effects of empagliflozin, as compared with placebo, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high risk for cardiovascular events who were receiving standard care, were examined.

The EMPA-REG OUTCOME trial was a randomized, double-blind, placebo-controlled trial to assess the effect of once daily empagliflozin (at a dose of either 10 mg or 25 mg) versus placebo on cardiovascular events in adults with type 2 diabetes at high cardiovascular risk against a background standard of care. Patients were treated at 590 sites in 42 countries. The trial continued until an adjudicated primary outcome event had occurred in at least 691 patients.

Eligible patients with type 2 diabetes were adults with a body mass index of 45 or less and an estimated glomerular filtration rate (eGFR) of at least 30ml per minute per 1.73m^2 of body-surface area,

according to MDR criteria. All the patients had established cardiovascular disease and had received no glucose-lowering agents for at least 12 weeks before randomization and had a glycated hemoglobin level of at least 7.0% and no more of 9.0% or had received stable glucose lowering therapy for at least 12 weeks before randomization and had a glycated hemoglobin level of at least 7.0% and no more than 10.0%.

Eligible patients underwent a 2-week open-label, placebo run-in period in which background glucose lowering therapy was unchanged. Patients meeting the inclusion criteria were then randomly assigned in a 1:1:1 ratio to receive either 10 mg or 25 mg of empagliflozin or placebo once daily.

Background glucose-lowering therapy was to remain unchanged for the first 12 weeks after randomization, although intensification was permitted if the patient had a confirmed fasting glucose level of more than 240 mg/dl. In cases of medical necessity, dose reduction or discontinuation of background medication could occur. After week 12, investigators were encouraged to adjust glucose-lowering therapy at their discretion to achieve glycemic control according to local guidelines. Throughout the trial, investigators were encouraged to treat other cardiovascular risk factors (including dyslipidemia and hypertension) to achieve best available standard of care according to local guidelines. Patients were instructed to attend the clinic at prespecified times, which included a follow up visit 30 days after the end of treatment.

The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke. The key secondary outcome was a composite of the primary outcome plus hospitalization for unstable angina.

Safety was assessed on the basis of adverse events that occurred during treatment or within 7 days after the last dose of a study drug. Adverse events of special interest included confirmed hypoglycemic adverse events, and adverse events reflecting urinary tract infection, genital infection, volume depletion, acute renal failure, bone fracture, diabetic ketoacidosis, and thromboembolic events.

A total of 7.028 patients underwent randomization from September 2010 through April 2013. Of these patients, 7.020 were treated and included in the primary analysis.

At baseline, demographic and clinical characteristics were well balanced between the placebo group and the empagliflozin group. According to the inclusion criteria, more than 99% of patients had established cardiovascular disease, and patients were well treated with respect to the use of lipid-lowering therapy and antihypertensive medications at baseline. The median duration of treatment was 2.6 years, and the median observation time was 3.1 years; both durations were similar in the pooled empagliflozin group the placebo group.

The primary outcome occurred in a significantly lower percentage of patients in the empagliflozin group [490 of 4.687(10.5%)] than in the placebo group [282 of 2.333 (12.1%)] (hazard ratio in the empagliflozin group, 0.86: 95.02% confidence interval, 0.74 to 0.99: $P<0.001$) for non-inferiority and $P= 0.04$ for superiority.

The key secondary outcome occurred in 599 of 4.687 patients (12.8%) in the empagliflozin group and 333 of 2.333 patients (14.3%) in the placebo group (hazard ratio, 0.89: 95% confidence interval, 0.78 to 1.01; $P< 0.001$) for noninferiority and $P=0.08$ for superiority.

As compared with placebo, empagliflozin resulted in a significant lower risk of death from cardiovascular causes (hazard ratio, 0.62; 95% confidence interval, 0.49 to 0.77; $P<0.001$), death from any cause (hazard ratio, 0.68; 95% confidence interval, 0.57 to 0.82, $P<0.001$) and hospitalization for heart failure (hazard ratio, 0.65; 95% confidence interval, 0.50 to 0.85; $P=0.002$). All categories of death from cardiovascular causes contributed to the reduction in cardiovascular death in the empagliflozin group. There were no significant between-group differences in the occurrence of myocardial infarction or stroke. Myocardial infarction was reported in 4.8% of patients in the empagliflozin group and 5.4% of those in the placebo group, and stroke in 3.5% and 3.0% of patients, respectively.

For the primary and key secondary outcomes, hazard ratios for the comparison between the 10 mg dose of empagliflozin versus placebo and the 25 mg dose versus placebo were virtually identical to those in the pooled analysis, but in the individual dose effects were not significant, owing to the smaller number of outcome events in the individual groups.

In prespecified sensitivity analyses based on events that occurred within 30 days after last dose of a study drug, results for the primary outcome, car-

diovascular death, myocardial infarction and stroke were consistent with the primary analyses, and the point estimate for the hazard ratio for stroke was closer to 1.00.

After 12 weeks, during which glucose-lowering therapy was to remain unchanged, the adjusted mean differences in the glycated hemoglobin level between patients receiving empagliflozin and those receiving placebo were -0.54 percentage points (95 confidence interval, -0.58 to -0.49) in the 10 mg group and -0.60 percentage points (95 confidence interval, -0.64 to -0.55) in the 25 mg group.

At week 94, the adjusted mean differences in the glycated level between patients receiving empagliflozin and those receiving placebo were -0.42 percentage points (95% confidence interval, -0.48 to -0.36) and -0.47 percentage points (95 confidence interval, -0.54 to -0.41), respectively. At week 206, the differences were -0.24 percentage points (95 confidence interval, -0.40 to -0.08) and -0.36 percentage points (95% confidence interval, -0.51 to -0.20).

Over the course of the study, empagliflozin, as compared with placebo, was associated with small reductions in weight, waist circumference, uric acid level, and systolic and diastolic blood pressure with no increase in heart rate and small increases in both LDL and HDL cholesterol. A higher percentage of patients in the placebo group received additional glucose-lowering medications (including sulfonylurea and insulin), antihypertensive medications (including diuretics), and anticoagulants during the trial, with no between-group difference in the receipt of lipid-lowering drugs.

The proportion of patients who had adverse events, serious adverse events, and adverse events leading to the discontinuation of a study drug were similar in the empagliflozin group and the placebo group. Genital infection was reported in a higher percentage of patients in the pooled empagliflozin group. The proportions of patients with confirmed hypoglycemic adverse events, acute renal failure, diabetic ketoacidosis, thromboembolic events, bone fracture, and events consistent with volume depletion were similar in the two study groups.

There were no relevant changes in electrolytes in the two study groups. Hematocrit values were higher in the empagliflozin groups than in the placebo group (mean[SD±]changes from baseline, 4.8%±5.5% in the group receiving 10 mg of empagliflozin, 5.05 (3%) in the group receiving 25 mg of empagliflozin, and 0.9±4.7% in the placebo group).

Benefits of empagliflozin were observed in a population with established cardiovascular disease in whom cardiovascular risk factors, including blood pressure and dyslipidemia, were well treated with the use of renin-angiotensin-aldosterone system inhibitors, statins, and acetylsalicylic acid. The reductions in the risk of cardiovascular death in the empagliflozin group were consistent across subgroups according to baseline characteristics.

Notably, reductions in the risks of death from cardiovascular causes and from any cause occurred early in the trial, and these benefits continued throughout the study. The relative reduction of 32% in the risk of death from any cause in the pooled empagliflozin group means that 39 patients (41 in the 10 mg group and 38 in the 25 mg group) would need to be treated during a 3-year period to prevent one death, but these numbers cannot be extrapolated to patient populations with other clinical characteristics.

Even though investigators were encouraged to adjust glucose-lowering therapy according to local guidelines, many patients did not reach their glycemic target, with an adjusted mean glycated hemoglobin level at week 206 of 7.81% in the pooled empagliflozin group and 8.16% in the placebo group. EMPA-REG OUTCOME trial was designed to assess the specific effects of empagliflozin on clinical outcomes, and the mechanisms behind the observed benefits are speculative. It is speculated that the mechanisms behind the cardiovascular benefits of empagliflozin are multidimensional and possibly involve changes in arterial stiffness, cardiac function, and cardiac oxygen demand (in the absence of sympathetic nerve activation), as well as cardiorenal[21] effects, reduction in albuminuria[20], reduction in uric acid[13-20], and established effects on hyperglycemia, weight, visceral adiposity and blood pressure[13-20].

This trial provides data to support the long term use of empagliflozin, as well as strong evidence for a reduction in cardiovascular risk. As observed in previous trials, genital infection was more common in patients treated with empagliflozin.

Concern has been expressed about the renal safety of inhibitors of sodium-glucose cotransporter 2 over time. However, the percentage of patients with acute renal failure was lower in the empagliflozin groups than in the placebo group, and

renal function was maintained with empagliflozin.

In conclusion, patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin had significantly lower rates of the primary composite cardiovascular outcome and of death from any cause than did those in the placebo group when the study drugs were added to standard care.

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Arterial Hypertension in Diabetes Mellitus

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Hypertension is very common among patients with diabetes mellitus (DM), with a prevalence approximately twice that of the non-diabetic population, and may precede the onset of diabetes[1,2]. The prevalence of hypertension is further increased in patients with type 2 diabetes and renal disease, as manifested by elevated urinary albumin excretion rates, compared with patients with type 2 diabetes and no evidence of renal involvement (80% of the patients, ranging from 71% of patients with normal urinary albumin excretion - UAE £30 mg/day- to 93% in patients with macroalbuminuria - UAE^3 300 mg/day)[3].

The insulin resistance is the main mechanism which leads to cardiovascular disease through hyperglycemia, hyperinsulinemia, hypertension, dyslipidemia, decreased fibrinolytic activity (PAI-1), endothelial dysfunction, subclinical vascular inflammation – oxidative stress and microalbuminuria[4,5].

The insulin resistance is also the major pathophysiology mechanism of hypertension in diabetics since it leads to volume expansion and vascular resistance through increased activity of sympathetic nervous system and rennin-angiotensin – aldosterone system[6].

In the UK Prospective Diabetes Study (UKPDS) the relation between systolic blood pressure over time and the risk of macrovascular or microvascular complications in patients with type 2 diabetes was considered. Rates for both myocardial infarction and microvascular endpoints were strongly associated, to a similar degree, with increasing systolic blood pressure. Each 10 mmHg decrease in updated mean systolic blood pressure was associated with reductions of risk of 11% for myocardial infarction (14% to 7%, $P<0.0001$), and 13% for microvascular complications (16% to 10%, $P<0.0001$). Furthermore, was considered the relation between exposure to glycemia over time and the risk of microvascular or macrovascular complications in the same patients. The incidence of clinical complications was associated significantly with glycemia. Each 1% reduction in updated mean HbA1c was associated with reductions in risk of 14% for myocardial infarction (21% to 8%, $P<0.0001$), and 37% for microvascular complications (41% to 33%, $P<0.0001$)[7]. Both in UKPDS study (1998), as in the Steno-2 study (1999), it was established that a multifactorial and intensive treatment of all car-

diovascular risk factors in patients with DM is associated with a huge reduction in micro- & macrovascular complications of DM (63% and 53% respectively). Followed by a 10-year post-interventional benefit, which was called as phenomenon of inherited effect[8,9]! However the ADVANCE trial was the study according to the results of which, blood pressure (BP) should be routinely treated to the level of optimal normal if not and lower (<130/80 mmHg), if tolerated, in all patients with DM[10]. On the other hand, the ACCORD study revealed contradictory results according to which a reduction in systolic BP<120 and diastolic BP<70 mmHg with the intensive versus the standard procedure (140 mmHg vs < 120 mmHg) was not associated with statistically significant benefit in reduction of the primary outcome, a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. There were also no differences in any of the secondary outcomes except for a reduction in stroke. However, the incidence of stroke in the group treated to lower than 140 mmHg was much lower than expected, so the absolute difference in fatal and nonfatal stroke between the 2 groups was only 0.21% per year. Moreover, the glucose-lowering arm of the study (intensive glucose control with a target of HbA1c <6%) was prematurely discontinued due to a rise in hypoglycemia and cardiovascular episodes (~35%)[11,12].

Based on the contradictory results of the various studies in hypertensive diabetics and the fact that just in one study, the antihypertensive treatment reduced the mean systolic BP<130 mmHg (with only partial benefit micro- and macrovascular complications), the European Society of Hypertension / European Society of Cardiology issued the revised guidelines at 2009 as reappraisal of European guidelines on hypertension management[13]. The most recent Guidelines —both European and American— confirm the Reappraisal of European guidelines on hypertension management, recommending higher blood pressure levels target since there are no enough data to support that a lower blood pressure actually reduces the cardiovascular events (Fig. 1, Fig. 2)[14,15].

Over the past 30 years many guidelines about

Blood pressure goals in hypertensive patients			
Recommendations	**Class[a]**	**Level[b]**	**Ref/[c]**
A SBP goal < 140 mmHg:			
a) is recommended in patients at low-moderate CV risk;	I	B	266, 269, 270
b) is recommended in patients with diabetes;	I	A	270, 275, 276
c) should be considered in patients with previous stroke or TIA;	IIa	B	296, 297
d) should be considered in patients with CHD;	IIa	B	141, 265
e) should be considered in patients with diabetic or non-diabetic CKD	IIa	B	312, 313
In elderly hypertensives less than 80 years old with SBP≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg	I	A	265
In fit elderly patients less than 80 years old SBP values <140 mmHg may be considered, whereas in the fragile elderly population SBP goals should be adapted to individual tolerability	IIb	C	–
In individuals older than 80 years and with initial SBP≥160 mmHg, it is recommended to reduce SBP to between 150 and 140 mmHg provided they are in good physical and mental conditions	I	B	287
A DBP target of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended. It should nevertheless be considered that DBP values between 80 and 85 mmHg are safe and well tolerated	I	A	269, 290, 293

CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; SBP, systolic blood pressure; TIA, transient ischaemic attack.
[a]Class of recommendation
[b]Level of evidence
[c]Reference(S) supporting levels of evdence

Journal of Hypertension 2013; 31: 1281-1357

Fig. 1. *ESC/ESH Guidelines for Management of Hypertension.*

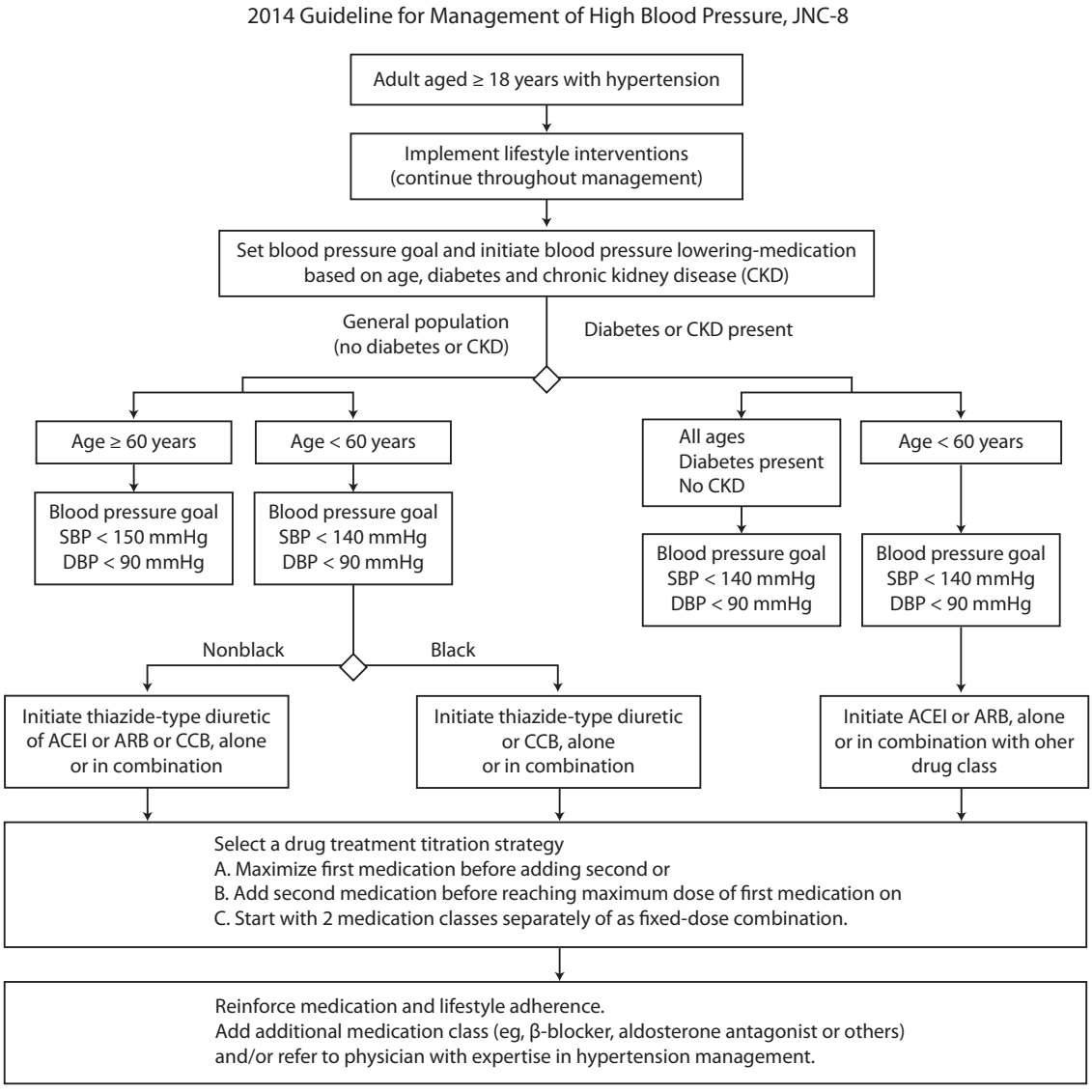

Fig. 2. *Guidelines for Management of High Blood Pressure, Join National Committee-8 (JNV-VIII).*

BP control in hypertensive diabetics have appeared. It is remarkable that for the first time in these recent guidelines, patients are classified according to their age with regards to the BP levels target. Also, the initiation of antihypertensive treatment is not only determined by the absolute levels of BP but also by the total cardiovascular risk as it is calculated by several scores (Framingham, Score, etc).

The most recent consensus report on BP by the American Diabetes Association (ADA) has also evaluated all recent data from the main trials and meta-analyses. The conclusion is the a BP target of 140/90 mmHg that is sustained at these levels and if the patient agrees and can tolerate BP reductions to levels between 125-130 mmHg for systolic BP, every effort should be done to achieve this level since it is associated with fewer cardiovascular events and reduced mortality[16]. Recently completed the SPRINT Study with somewhat similar protocol as in ACCORD Trial, but in non-diabetic patients, showed almost one-quarter reduction in all-cause mortality and one-third reduction of cardiovascular events with systolic BP goal ≤120 mmHg[17]. However in SPRINT Trial, BP was measured using a research technique (SPRINT specified 5 minutes of seated rest in a quiet room followed by 3 oscillometric measurements without an observer in the room). Furthermore, patients with DMor prior strokewere

excluded and frail elderly were underrepresented (28.2%). The fact that the study was open label in a strategy close to usual care with frequent visits may have helped to adjust the antihypertensive treatment if serious side effects occurred and thus minimized the risk of events. So, generalizability of the findings of SPRINT to patients with DM, stroke and to frail elderly is problematic[17].

With regard the initial choice of antihypertensive therapy –beyond the non-pharmaceutical measures with lifestyle changes that offers a similar benefit with monotherapy (~20-38 mmHg)– it is also based on the coexisting conditions (co-morbidities). The initial choice of a certain antihypertensive category will be based on the effectiveness and safety of them (individualized) and taking into account the coexistence of subclinical target organ damage, overt cardiovascular or renal disease, the specific beneficial properties (pliotropic actions) of each class of drug beyond the reduction of BP, the selective organ protection of the heart, kidneys, brain, peripheral vessels, the coexistence of conditions for which some medicines are contraindicated and the likelihood of interactions between other drugs and the favorable metabolic profile, better tolerance / differences in the appearance of side effects of the newer drugs[18]. Renin-angiotensin-aldosterone system (RAAS) blocker is recommended in the treatment of hypertension in DM, particularly in the presence of proteinuria or micro-albuminuria. However, ACE inhibitors and angiotensin receptor blockers are only mandated for those with kidney disease (eGFR < 60 ml/min/ 1.73 m^2) with > 300 mg/day of albuminuria. They are not preferred in normotensives with normal kidney function with or without microalbuminuria or hypertensives without albuminuria. The cornerstone is achieving BP reduction and not the drug class![18]

When the systolic BP is > 20 mmHg or diastolic BP > 10 mmHg from BP target, we can use a combination (usual fixed combination which increase the compliance of the patients) of 2 antihypertensive drugs. Since resistant hypertension in diabetics is more often than hypertensive patients without DM, the average number of antihypertensive drugs are at least three[19,20]. The most appropriate combination seems to be the combination of a RAAS blocker with a calcium channel antagonist –in particular in hypertensive diabetics– since despite the similar reduction of BP in comparison with other combinations (e.g. RAAS blocker with diuretics), there is a higher reduction in cardiovascular events and fewer cases of newly-diagnosed DM[21,22]. On the other hand, as in case of some antihypertensive classes which exert a beneficial effect on the glycemic profile, so some new classes of antidiabetic drugs such the Sodium – Glucose Contransporter-2 (SGLT2) inhibitors and the incretin mimetics and in particular the GLP-1 Agonists have a beneficial effect on BP by lowering these levels[22,23]. In particular, they exert vasodilatation, diuresis, sodium excretion, weight reduction while they also improve the aortic stiffness and the sodium-sensitivity to sodium-resistance (increased in DM)[23,24].

Despite the fact that currently various antihypertensive drugs and their fixed combinations are available, it is striking that the BP control –and especially in diabetics– has remained low (1 out of 3 patients, namely ~33%) worldwide over the last 15-20 years. Chronotherapy could contribute to this issue since chronotherapy investigate the administration of the correct amount of an active substance through the appropriate pathway at an appropriate time. Some data suggest that nocturnal rather than daytime dosing of antihypertensive agents may have beneficial effects on consequent cardiovascular outcomes[25,26]. In this frame, Hellenic-Anglo Research into Morning Or Night antihypertensive drug deliverY Trial (HARMONY Trial) designed to evaluate whether Ambulatory BP Monitoring (ABPM) levels differ by timing of drug dosing, as a possible explanation for these observations and theory of chronotherapy. According to its preliminary results, in patients with stable BP levels and hypertension diagnosed at least one year ago, the timing of antihypertensive drug administration (morning or evening) did not effect the mean 24 hour ABPM levels recorded[27].

In conclusion, the coexistence rate of hypertension in DM is much higher and increases synergistically the risk cardiovascular events and chronic kidney disease. Physicians should strictly regulate all risk factors in any hypertensive diabetic patient in order to reduce the total cardiovascular risk and to avoid both macrovascular complications and microvascular complications and in particular albuminuria and its progress to end stage renal disease. The percentage of BP control is very poor in total of hypertensives and especially in diabetics. It is usually necessary to combine antihypertensive drugs including as one component RAAS blockers since they have nephro- and cardio-protection!

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Hellenic Diabetological Chronicles 31, 2: 107, 2018

Diabetes Mellitus, hypertension and nephropathy – A vicious triangle

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Diabetes mellitus is associated with hypertension and nephropathy which have a great clinical impact on the course of the disease and its outcome. Hypertension and nephropathy reflect profound macro- and microangiopathic alterations and damage of a diabetic patient which the potential to aggravate each other in a reciprocal manner. In this constellation diabetes, hypertension and nephropathy manifest as a vicious triangle that is associated with increased morbidity and mortality, mainly due to increased cardiovascular events and deaths. In addition to adequate treatment of hyperglycemia, blood pressure control and nephroprotection by the use lowering of intraglomerular pressure are of paramount importance. Proteinuria can be regarded as a strong biomarker that predicts both morbidity and mortality in diabetic patients with hypertension and nephropathy. Recent studies suggest that excretion of active serine proteases in proteinuria causes renal sodium retention leading to salt-sensitive hypertension. Lowering of proteinuria by the use of renin-angiotensin-system blockers has been shown to improve clinical outcomes in these patients. Currently, SGLT2 inhibitors while reducing proteinuria emerge as a protective drug class in diabetes that both prevent cardiovascular events and progression of diabetic nephropathy.

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Diabetes Mellitus and Cardiac Function: beyond Ischemic Heart Disease

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From a clinical perspective, quite often in day-to-day clinical practice many patients with Diabetes Mellitus come along in the emergency room with symptoms of heart failure or/and pulmonary edema. Many times the usual diagnosis after exclusion of ischemic heart disease, is Left Ventricular DiastolicDysfunction (LVDD) with preserved left ventricular systolic function. Two distinguished mechanisms seem to be implicated after the exclusion of hypertension, also. Those are diabetic cardiomyopathy and diabetic cardiovascular autonomic neuropathy. In this context, the clinical course of cardiac diastolic dysfunction in diabetes mellitus progresses from subclinical cardiac abnormalities, to severe diastolic heart failure with normal ejection fraction and eventually to systolic dysfunction and at the end by heart failure with reduced ejection fraction. In current review we summarize data about the two aetiopathogenetic mechanisms which lead to LVDD as first manifestation and later to heart failure with reduced left ventricular ejection fraction. Moreover, we summarize clinical evidence that provide substantial indications to improve therapeutic management in early stages of LVDD and could be associated with improved clinical outcome in long-term duration of DM.

Heart failure and its management is the main and seriously growing up medical problem and heath problem for the entire population. Disorders of hyperglycemia, hypertension, obesity and dyslipidemia occur more often in either alone or in various combinations in patients with Diabetes Mellitus and they increase substantially the risk of developing diastolic or/and systolic Left Ventricular Dysfunction. The final result is the occurrence of the Heart Failure (HF). Furthermore, many of the antidiabetic drugs used to control hyperglycemia are relatively 'contraindicated' in HF as has been reported from large international multicenter studies. Some of them could cause or/and precipitate cardiac dysfunction, although others have a beneficial effect.

Early assessment, diagnosis and management of cardiac dysfunction during the course of diabetes probably will add to the most reduction of cardiovascular events due to ventricular dysfunction and heart failure. Moreover, it is important to address the underlying cause of heart failure, because the specific etiology determines the choice of treatment.

Diabetic cardiomyopathy is initially characterized by myocardial fibrosis, dysfunctional remodeling, and associated diastolic dysfunction, later by systolic dysfunction, and eventually by clinical heart failure. Impaired cardiac insulin metabolic signaling, mitochondrial dysfunction, increases in oxidative stress, reduced nitric oxide bioavailability, elevations in advanced glycation end products and collagen-based cardiomyocyte and extracellular matrix stiffness, impaired mitochondrial and cardiomyocyte calcium handling, inflammation, renin-angiotensin-aldosterone system activation, cardiac autonomic neuropathy, endoplasmic reticulum stress, microvascular dysfunction, and a myriad of cardiac metabolic abnormalities have all been implicated in the development and progression of diabetic cardiomyopathy. Molecular mechanisms linked to the underlying pathophysiological changes include abnormalities in AMP-activated protein kinase, peroxisome proliferator-activated receptors, O-linked N-acetylglucosamine, protein kinase C, microRNA, and exosome pathways.

Diabetic Cardiac Autonomic Neuropathy (DCAN) is a secondary complication related to poor glycemic control and includes abnormalities in heart rate control, vascular hemodynamics, andcardiac structure and function. An early characteristic of Cardiac Autonomic Neuropathyis reduction of parasympathetic activity with an imbalance toward relatively higher Sympathetic Nervous System (SNS)activity. In this regard, activation of the SNS enhances β-1 adrenergic receptor (β1) signaling that promotes cardiac hypertrophy, interstitial fibrosis, cardiomyocyte apoptosis, and impaired function.

The treatment of LVDD should relieve symptoms and increase longevity. Unfortunately, to date, studies of neurohormonal blockade in patients with LVDD have failed to show a mortality benefit or a clear improvement in quality of life. Inhibitors of the RAAS and sympathetic nervous system should continue to be used in the population of patients with LVDD who have diabetes mellitus despite the fact that the use of these drugs for the primary treatment of LVDD remains unsupported by the available evidence from large studies. But in small studies with well characterized patients ACE-Inhibitors have been shown to improve both LVDD and Cardiac Autonomic Dysfunction simultaneously after one year of treatment.

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Incretin based therapies – novelties to learn 2018

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Incretin based therapies comprising the orally active dipeptidyl peptidase-4 inhibitors (DPP-4i) and the injectable glucagon-like peptide-1 receptor agonists (GLP-1RA) have been introduced into type 2 diabetes therapy twelve years ago. They utilize the action of the hormone GLP-1 that stimulates insulin secretion and inhibits glucagon secretion in a plasma glucose-dependent manner. DPP-4i inhibit the ubiquitous enzyme DPP-4 that physiologically degrades and inactivates GLP-1 as main substrate and therefore elevate endogenous GLP-1 plasma concentrations appr. 3-fold. GLP-1RA lead to an 8-10-fold elevation.

DPP-4i have a very low hypoglycaemia risk and are body weight neutral. In many comparative studies they have shown similar efficacy as sulfonylureas. Cardiovascular safety studies have demonstrated cardiovascular safety regarding a composite primary endpoint consisting of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke. DPP-4i are mostly used as second line oral medication after metformin failure in a combination with metformin. Fixed dose combinations for metformin and DPPi are available. In patients with metformin intolerance or metformin contraindications (e.g. renal failure) they are also often used in monotherapy.

GLP-1RA also have a very low hypoglycemia risk. They allow body weight loss that is explained by two mechanisms: 1) GLP-1 acts as a mediator of satiety in the central nervous system and 2) slows gastrointestinal motility facilitating the sensation of fullness (and nausea as adverse event). GLP-1RA are also mainly used after metformin failure, mostly in patiens with obesity when body weight loss is another important treatment goal. Short acting (for daily dosing) or long acting (for once weekly dosing) substances can be used. One GLP-1RA has also received approval for the treatment of obesity independently of type 2 diabetes. Two long acting GLP-1RA have shown superiority regarding cardiovascular outcomes in comparison to standard antidiabetic treatment. GLP-1RA have also a beneficial potential in the use of a combination therapy with insulin treatment. This combination is often less complex than an insified insulin regimen, leads to less hypoglycaemic episodes and is more favorable regarding the body weight gain observed during insulin therapy.

A review of both substance classes, the DPP-4i and GLP-1RA

is given regarding their present usage and placement in the treatment guidelines for type 2 diabetes. Their potential in combination therapies is presented, especially in later stages of type 2 diabetes in combination with insulin or with SGLT-2 inhibitors. Furthermore, novel data that open up potential novel indications and treatment options are presented. For DPP-4i this includes an overview on other substrates for DPP-4 besides GLP-1 and the potential consecutive clinical implications arising. For the GLP-1RA novel forms of applications are introduced.

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Hypoglycemia: Mechanisms and possibilities of prevention

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Introduction

Intensive glucose control reduces the risk for the development of the microvascular complications of diabetes[1,2]. There is also evidence that suggests that intensive glycose control for 6.5 years reduces the risk of macrovascular complications in type 1 diabetes, 30 years later[3]. Therefore tight glycemic control is recommended in patients with diabetes. One of the limiting factors in achieving tight glycemic goals in patients treated with insulin and insulin secretagogues is hypoglycemia[4].

Episodes of severe hypoglycemia,where a person with diabetes requires the assistance of another person for treatment, are relatively easy to track. However it is rather common that the persons with diabetes who do not have severe neuroglycopenia do not always confirm that their blood glucose is low when they have symptoms associated with hypoglycemia or, because episodes are asymptomatic. The International Hypoglycemia Study Group (IHSG) recently published a position statement on the glucose levels that should be used to define hypoglycemia[5]. The statement has been adapted by the American Diabetes Association and the European Association for the Study of Diabetes (Table 1).

Table 1.

GLUCOSE VALUE	
<70mg/dl	Alert value to take action to prevent further fall in plasma glucose
<54 mg/dl	Sufficient low to indicate serious clinically importan thypoglycemia
Any low value	Severe cognitive impairement requiring external assistance for recovery

Prediction of Hypoglycemia

Intensive glucose control has been linked with increased risk of severe hypoglycemia. The incidence of severe hypoglycemia in the

DCCT trial the incidence of severe hypoglycemia was three times higher in the intensive treatment group than in the conventional[2]. Like wise in studies with type 2 diabetes like ACCORD, VADT[6,7], the rate of hypoglycemia requiring medical assistance was three times higher in the intensive therapy group compared tothe standard therapy. Both in type 1 and type 2 diabetes patient those with an A1c <6,5% and >9% have the same risk of hypoglycemia[8].

In patients with type 2 diabetes, hypoglycemia is associated with several risk factors including older age, diabetes duration, co-morbidities, intensified treatment, current insulin treatment and duration of insulin treatment. Moreover in theACCORD study severe hypoglycemia was associated with sex, race, serum creatinine, age, duration of diabetes, body mass index, albuminuria, educational level, Insulin use and higher HbA1c[9]. Recent analysis of the ACCORD indicated that c-peptide or GAD antibodies may predict severe hypoglycemia and mortality in type 2 diabetes[10].

Consequencies of Hypoglycemia

1. Cardiovascular disease and mortality

Severe hypoglycemia has been associated with increased risk of cardiovascular death both in the ACCORD and the ADVANCE trial. The mechanisms of increased mortality among patients with severe hypoglycemia is under current investigation but there is evidence to support that cardiac ischemia or arrythmias may play a role especially in patients with cardiac autonomic neuropathy[11]. The catecholamine release induced by hypoglycemia have been described to cause cardiac arrythmia, increased thrombogenesis, inflammation and vasoconstriction leading to cardiovascular disease and death.

2. Cognition

In the DCCT trial there was no evidence of long term declines in cognitive function in patients with type 1 diabetes who were followed for an average of 18 years despite high rates of recurrent severe hypoglycemia[12]. In the ACCORD study, subjects in the lowest tertile of performance on a cognitive test at baseline had a significantly higher risk of experiencing hypoglycemia during the subsequent twenty months compared to the subjects who performed better on the same cognitive test[13].

From the available trials it is not clear if severe hypoglycemia causes dementia or if pre-clinical forms of cognitive dysfunction increase the risk of severe hypoglycemia.

3. Health Economics and Quality of Life

Hypoglycemia has significant health care economic burden on the society through frequent emergency room visits, ambulance utilization and hospitalization costs. Hypoglycemia also affects the economic wellbeing of the individual. Recurrent hypoglycemic episodes result in lost work-time and reduced work productivity[14].

The fear of hypoglycemia also has a significant impact on the quality of life of patients and their families. The fear often limits adherence to treatment regimens leading to persistent hyperglycemia both in type 1 and type 2 diabetes[15].

Physiology and Pathophysiology

In normal individuals plasma glucose is kept within a narrow range (70-100 mg/dl). When the plasma glucose fall below this threshold the body initiates physiologic responses in order to raise the plasma glucose level. Plasma glucose <80 mg/dl reduces the secretion of insulin from the pancreas which ensures maintenance of normoglycemia. If blood glucose continues to fall, glucagon is released at a blood glucose level of 65 mg/dl. At this glucose level the sympathetic nervous system gets activated resulting in epinephrine and norepinephrine release. These responses increase hepatic glucose production and reduce glucose uptake into muscle and fat to achieve return to normoglycemia. In addition, the activation of the sympathetic nervous system leads to the appearance of adrenergic symptoms[16].

In patients with type 1 diabetes or advanced type 2 diabetes where pancreatic beta cell function is absent, the first defense mechanism preventing hypoglycemia is lost. These patients are unable to reduce the secretion of insulin since insulin is injected. They also lose the ability to release glucagon in response to hypoglycemia and they depend only in the activation of the sympathoadrenal system to prevent hypoglycemia which is also diminished after almost 15 year duration of the disease (17 gerich). Consequently they get exposed to repeated hypo-

glycemias which reduces the glucose level at which the sympathetic response is elicited and reduce the magnitude of the response. As a result patients may not trigger the counterregulatory response until the blood glucose level is below the level associated with neuroglycopenia[18]. This situation is called hypoglycemia unawareness and is associated with 6-fold increase of the risk of iatrogenic hypoglycemia[19].

Prevention of Hypoglycemia

The ADA working group on hypoglycemia recommends that persons with diabetes become concerned about the possibility of developing hypoglycemia when self-monitoring concentration is falling rapidly or equal or below 70 mg/dl[20]. This concentration should be taken as an alert value to take action to prevent further fall in plasma glucose.

1. Education

Patients need to be educated in understanding the risk for developing hypoglycemia so they are able to prevent it. The greatest risk is excessive insulin on board for their physiological needs (insulin or secretagogues), especially when exogenous glucose delivery is decreased (missed meals, fasting, gastroparesis or celiac disease), when glucose utilization is increased (shortly after exercise), when endogenous glucose production is decreased (alcohol ingestion), when insulin sensitivity is increased (middle of the night, weight loss) or when insulin clearance is decreased (renal failure). Education should be provided in individual sessions or group classes (21 Amiel). Programs like DAFNE and BGAT (Blood Glucose Awareness training) have been shown to be effective in reducing the risk of hypoglycemia[22].

2. Technology

Continuous glucose monitoring (CGM) with real time glucose readings, is an important tool in assessing glucose trends while displaying the direction and rate of change of interstitial blood glucose. The recently published DIAMOND trial showed that CGM use, decreased the time spent with glucose values less than 70 mg/dl during the day and night in patients with type 1 diabetes[23].

Recent advances in technology, include continuous glucose monitors coupled to an insulin pump. In one system, insulin infusion is suspends for up to two hours if glucose falls into hypoglycemic range[24]. In the latest sensor augmented pumps insulin infusion is suspended if the if user is below 140 mg/dL and is predicted to be below 70 mg/dl in 30 min and resumes if user is above 80 mg/dL and is predicted to be at or above 110 mg/dl in 30 min and insulin has been suspended for at least 30 min[25].

Data on the Artificial Pancreas show consistent reduction in overnight low blood glucose index and a shortening of time below 70 mg/dl over a 24 hr period by about 20 minutes compared with control treatment. Incidence of severe hypoglycaemia is very low[26].

3. Transplantation

Pancreas and, now, islet transplants can effectively prevent hypoglycemia and restore normoglycemia and may stabilize the complications of T1D. Patients with T1D who undergo an islet or a pancreas transplant exhibit recovery of physiologicislet cell hormonal responses to insulin-induced hypoglycemia whereby endogenous insulin secretion is suppressed and glucagon secretion restored, although in islet transplant recipients, the glucagon response remains partial likely due to lower islet mass compared to organ transplantation. Both islet and pancreas transplant recipients also have improved epinephrine and normalized autonomic symptom responses to hypoglycemia, providing evidence of amelioration of hypoglycemia-unwareness[27-29].

In type 2 diabetes hypoglycemia can be prevented with avoidance of secretagogue antidiabetic drugs and use of premixed insulin regimens. The use of metformin, DPP-4 inhibitors, SGLT-2 agonists and their combinations are preferred for the prevention of hypoglycemia[30].

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Impact of circadian disruption on energy balance and diabetes risk

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We are impressed but passive observers of the "metabolic big bang", resulting in the dual explosion of Obesity and type 2 Diabetes Mellitus throughout the developed and even the developing world. Diabesity, the new epidemic, has risen as a major public health problem since it greatly increases chronic diseases with huge human and socioeconomic burdens. Further comprehension of the underlying pathophysiology is an urgent need for the development of novel preventive and therapeutic strategies. Behavioral and environmental changes in modern societies act as circadian disruptors with detrimental effects on energy balance, body weight, wellbeing and overall health. Circadian disruption and sleep disorders emerged as new players in the field of Diabetes.

During the past decade, numerous data from experimental and epidemiological studies have suggested that delayed feeding, prolonged nocturnal activity and exposure to artificial light, excess use of self-luminous devices at nighttime, long-term and frequent shift work, reduced sleep duration and abnormal sleep architecture cause circadian misalignment. This, in turn, promotes central obesity, inflammation, insulin resistance, hypertension, cancer, depression and/or anxiety, neurodegenerative diseases, immunological disorders, hypertension, cardiovascular diseases and T2DM. Chronobiology was thrust into the spotlight with the 2017 Nobel Prize in Physiology or Medicine awarded to Jeffrey Hall, Michael Rosbash and Michael Young for the discoveries over the past 15 years of the genetic and molecular mechanisms of circadian rhythms and of their fundamental role in the regulation of cellular metabolism. In addition to recognizing their groundbreaking work, the Prize also served as: a) a call for further molecular and epidemiological research about the impact of sleep quantity and quality on health, b) a "social alarm" for humans neglecting their circadian clock and pushing their bodies beyond internal borders, since a disturbed clock becomes a potential ticking time bomb and c) a Roadmap to Metabolic Therapeutics, Chronopharmacology, Chronotherapy, Chrononutrition and other emerging applications. Living organisms, spanning from cyanobacteria to humans, are governed by common daily cycles known as circadian rhythms. They represent an evolutionarily conserved adaptation of cellular processes, physi-

ological functions and behavioral patterns to the predictable cycle of light and dark on Earth in order to optimize energy homeostasis. The word "circadian", introduced by Franz Halberg, is derived from Latin words *circa* = about and *diem* = day and literally means "about a day". Thus, circadian rhythms are endogenous, self- sustained oscillations of ~24hin the biological and biochemical landscape (tissue, cell, subcellular compartment as mitochondria, body temperature, blood pressure, levels of circulating hormones and metabolites, CNS outputs, gut microbiome, etc).

In mammals and humans, the circadian timing system is organized into a hierarchical manner with a central pacemaker or master circadian clock, located in the suprachiasmatic nuclei (SCN) of anterior hypothalamus and formed by a net of ~20,000 neurons. Light/Dark cycle is the most important timing cue (Zeitgeber) that sets SCN at a periodicity of ~24h. Transmission of light signals via the retinohypothalamic tract facilitates adaptation to the geographical location and daytime. In turn, SCN interacts with peripheral clocks, consisted of oscillators in various brain regions and peripheral organs including heart, lungs, liver, pancreas, kidneys, adipose tissue and endocrine glands. The SCN acts as the hypothalamic link between the retina and peripheral oscillators, entraining them to the Light/Dark cycle. Physical activity, nutrient availability, meal timing and GLP-1 release can reset peripheral clocks and crosstalk with SCN. Glucocorticoids, melatonin, neuroendocrine outputs and direct autonomic innervation are the main endogenous signalling mechanisms by which the SCN maintains alignment of central and peripheral oscillators. A main SCN–CRH–ACTH output drives a rise in adrenal glucocorticoids just before activity onset. This promotes arousal and alertness by enhancing liver gluconeogenesis. Melatonin is an endogenous hormone produced by the pineal gland exclusively at night (21.00-4.00) and responsible forinitiation and maintenance of sleep and circadian rhythmicity. Recent data support that it affects the insulin secretory activity of the pancreatic beta cells, hepatic glucose metabolism and insulin sensitivity. Additionally, melatonin exerts potent antioxidant, anti-inflammatory and oncostatic properties, especially in breast cancer. Reduced melatonin levels, mutations and/or genetic polymorphisms of the melatonin receptors *MTNR1B*are associated with an increased risk of developing type 2 DM.

Chronic exposure to artificial light at night (ALAN) in work, home and social life result in melatonin synthesis suppression, circadian misalignment and sleep/wake cycle disruption with sleep deprivation. The widely used electric lights, like Daylight White Fluorescent and energy-saving Compact Fluorescent ones, are richer in blue λ and suppress melatonin release when used within 1h of bedtime. A new source of ALAN is nighttime use of personal computers, mobile phones, electronic tablets, televisions, and internet world "surfing", a behavioral epidemic in adults, adolescents and school-aged children. ALAN pollution of urban areas is a modern threat for ecosystems and humans. Unfortunately, ALAN exposure occurs concomitantly with severe decrease of exposure to sunlight, whose blue-violet (446-484 nm) spectrum synchronizes the circadian clocks and whose UV-B (290-315 nm) spectrum stimulates vitamin D synthesis. Vitamin D insufficiency or deficiency in combination with melatonin suppression is a dual deleterious factor for health. The association of exposure to ALAN and higher BMI has been found statistically significant in both adults and paediatric populations.

At the cellular level, circadian oscillation is encoded by a transcription-translation feedback loop (TTFL) of interacting transcriptional factors known as clock genes.This family includes CLOCK, Bmal1, Per1, Per 2, Per 3, Cry1 and Cry2, RORα and REV-ERBα. The positive limb of the loop contains a heterodimer complex of CLOCK: BMAL1 which binds to E-box motifs and upregulates the transcription of circadian genes, including those from the cryptochrome family (Cry1 and Cry2) and the period family (Per1, Per2 and Per3). The negative limb of the loop contains protein products of the Per and Cry genes which heterodimerise to form PER–CRY and repress BMAL1: CLOCK activity. REV-ERBα and RORα control the timing and amplitude of BMAL1 expression and provide additional stability to the molecular oscillator. The CLOCK: BMAL1 complex stimulates mitochondrial biogenesis and mitophagy through activation of SIRT1 and plays a critical role in mediating the transcription of coactivators that regulate the synthesis of 25% of genes and most of the enzymes and hormones involved in glucose homeostasis, i.e., regulation of hepatic glu-

coneogenesis and pancreatic β-cell insulin secretion. Elegant studies demonstrate that the molecular circadian clock is coupled to metabolism at the cellular level, and that circadian mutant animals develop metabolic dysregulation, obesity, impaired glucose tolerance/diabetes and reduced lifespan. Obvious circadian disruption is found in shift workers (eg, airline crews, truck drivers, medical doctors, nurses, scientific technical staff, law enforcement and the military) and has been correlated with increased risk ofbreast and prostate cancer, increased BMI, IGT, DM2 and cardiovascular morbidity and mortality. However, the general public isexposed to ALAN, work schedules that conflict with an individual's chronotype (endogenous circadian preference) and "social jet lag" (changes in sleep patterns from the work days to nonwork days such as weekends).

Chronic sleep restriction is associated to increase of ghrelin levels, decrease of leptin levels and constantly increased cortisol levels resulting in unhealthy snacking, emotional overeating, less physical activity, central obesity and increased cardiometabolic risk.

There is a general belief, according to experimental data, that calorie intake throughout the day is preferable to late in the evening, but RCTs are lacking. The phrase "It is not only what and how much you eat, but also when you eat" sends a simple but important message to clinicians and patients. Another message is "more sleep and less blue light at night", as a clinical translation of circadian rythms disruption.

Future Meetings of Hellenic Association for the Study and Education of Diabetes Mellitus

The Hellenic Association for the Study and Education of Diabetes Mellitus is organizing:

- 26 January 2019, **Thessaloniki**
  Scientific Meeting "Diabetes Mellitus. A modern health problem"
  for Dietitians-Nutriotionists, Nursing and Paramedical Staff,
  Aristotle University Research Dissemination Center (KEDEA)

- 16-18 May 2019, **Thessaloniki**
  2nd Joint International Scientific Meeting "Diabetes Mellitus. Meet the Expert"
  Co-organisation with the University of Tübingen
  Hotel "Electra Palace"

- 28-29 June 2019, **Corfu**
  Scientific Meeting
  Therapeutic management of type 2 Diabetes Mellitus

- 11-12 October 2019, **Rhodes**
  Scientific Meeting
  Therapeutic management of type 2 Diabetes Mellitus

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  Επιστημονική Ημερίδα για Διαιτολόγους-Διατροφολόγους, Νοσηλευτικό και Παραϊατρικό Προσωπικό: «Σακχαρώδης Διαβήτης: Ένα σύγχρονο πρόβλημα υγείας»
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