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

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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.

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Άλλα άρθρα

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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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PROCEEDINGS OF THE 2nd Joint International Scientific Meeting "Diabetes Mellitus: Meet the Expert"

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2nd Joint International Scientific Meeting

"Diabetes Mellitus: Meet the Expert"

Co-organized by the Hellenic Association for the Study and Education of Diabetes Mellitus in collaboration with the Departmen of Internal Medicine IV of the Eberhard -Karls University of Tübingen, and the Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Germany

16-19 May 2019, Thessaloniki Greece

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The Antikythera Mechanism

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Generally

The Antikythera mechanism was a technologically amazing analogue computer. It was constructed 2.000 years ago and was used to calculate the exact position of the Sun, the Moon and possibly the planets in the sky. It calculated the phases of the Moon, predicted eclipses and indicated the date of the Panhellenic games. It had front and back doors, with astronomical, geographical and technological inscriptions covering much of the exterior of the Mechanism. Thanks to the innovative research techniques used, were read texts lost for over 2.000 years! All inscriptions are written in Greek. Its dimensions were approximately 30 × 20 × 10 cm –slightly larger than a current Laptop– and contained over 30 gears. It had three main dials, one on the front with two concentric scales, and two on the back in the form of spirals. It is as important for the evolution of technology as the Acropolis for the evolution of architecture. Similar ancient mechanism has not so far been found. This raises the reasonable question of what was the technical infrastructure the time when the Antikythera Mechanism was built and what happened to the knowledge and the art that it reveals.

The underwater excavation

In 1900 a party of sponge-fishers from the island of Syme discovered accidentally an ancient shipwreck off the coast of the island of Antikythera. The excavation began at the end of November 1900 and a few months later were recovered important findings, such as the famous Antikythera Ephebe, many of which are nowadays exhibited at the National Archaeological Museum of Athens. Among the findings, was the Antikythera Mechanism, which –broken, corroded and petrified after 2.000 years on the seabed– was going to

change the knowledge that we had so far on the technological skills of our ancestors. From Pergamon coins that were retrieved, the wreck is dated between 85 and 67 BC. The detailed form of the lettering of the Antikythera Mechanism can be dated to the second half of the 2nd Century BC, implying that the Mechanism was constructed during the period 150-100 BC.

An ancient calendar

On the back side of the Antikythera Mechanism, there were two main dials in the form of spirals. The lower back dial is a Saros eclipse-prediction dial, arranged as a four-turn spiral of 223 lunar months, with glyphs indicating eclipse predictions. The upper back dial is a 19-year calendar, arranged as a five-turn spiral of 235 lunar months. This calendar is known as the Metonic cycle by the Greek astronomer Meton of Athens who lived in the 5th century BC and had observed that at this period of 19 solar years the Moon returned to the same point in the sky with the same phase. At the subdivisions of the spiral are carved with fine art the ancient names of 12 months, repeated for the formation of the period of the 19 years. The names of the months are of Corinthian origin with the Corinthian colonies of northwestern Greece and Tauromenium in Sicily to be the leading contenders. A new font (True type fonts) has been constructed at the Aristotle University of Thessaloniki, reproducing the fine art letters.

The Panhellenic Crown Games

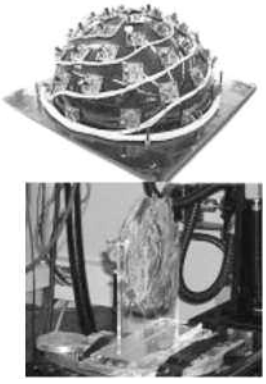
The subsidiary dial within the upper back spiral of the Antikythera Mechanism displayed the celebration year of the ancient Panhellenic crown games. Circumferentially to the dial have been read the words Olympia, Pythia, Isthmia, Nemea and Naa, while internally, in each quadrant, are indicated the four years of the Olympic cycle. All these games were crown games, with winners being rewarded with crowns (stephanoi).

The gears

The Antikythera Mechanism contained at least 30 cooperating gears and several pointers. On the front side, there were two concentric circular scales. The outer scale had 365 subdivisions and the names of the 12 Egyptian months in Greek. The inner scale had 360 subdivisions and the names of the 12 zodiac constellations. The operator, by turning a crank handle, moved the gears that in their turn rotated on the front side two pointers that indicated the position of the Sun and the Moon. Beneath the outer scale, which was removable, there were 365 holes. Every four years the operator could detach it and shift it by one hole, thus taking into account leap years. A rotating sphere, adapted with a crown to the pointer of the Moon, displayed the phases of the Moon. The movement of the Moon is not circular

but elliptical. The display of this movement, taking into account the anomaly caused by its eccentric orbit around the Earth, was achieved by the use of two eccentric gears, the axes of which are distanced by 1.1 mm. The lower gear has a pin that engages with a slot on the upper gear, forcing it thus to rotate by the pin-and-slot arrangement. The epicyclical movement of the upper gear tracked the motion of the Moon in the sky with great accuracy.

Innovative research techniques



During September 2005, the research division of Hewlett-Packard (HP Labs, California) sent to Athens three specialized scientists who recorded, using the innovative digital imaging mechanism PTM Dome, even faded and worn inscriptions and other details of the surface of the fragments of the Antikythera Mechanism. The Dome surrounded the fragment under examination and took a series of still photos from 50 different directions in order to analyze the three-dimensional structure of the surface. Thus it became possible to study details of the surface of the fragments even when they were not visible with the best systems of conventional and digital photography.

During October 2005, another team of specialists worked at the National Archaeological Museum. This group, from the cutting-edge company, X-Tek Systems, brought with the prototype of the very powerful new x-ray machine "Bladerunner", weighing 8 tons, maximum voltage 450 kVolt and resolution of one twentieth of a millimetre (50 mm). The three-dimensional images that were obtained when the fragments of the ancient mechanism were examined revealed internal details of gearing and inscriptions that remained hidden on the seabed of the Antikythera more than two thousand years.

Construction of the most representative model of Antikythera Mechanism

Over the last ten years, a research team of the Aristotle University of Thessaloniki, is studding the Antikythera Mechanism. The team consists of Prof. Seiradakis J. (School of Physics), Prof. Efstathiou K. (School of Mechanical Engineering), Dr. Anastasiou M. (School of Physics), Dr. Efstathiou M. (School of Mechanical Engineering). In this research program, the most representative up to today, models of the Antikythera Mechanism were constructed, in real dimensions and also in scale 3:1.

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Incretin based therapies: New cardiovascular data and development of novel molecules for the treatment of type 2 diabetes

Baptist Gallwitz

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Incretin based therapies were introduced for the treatment of type 2 diabetes in 2006 and comprise two classes of medications: the orally active DPP-4 inhibitors and the GLP-1 receptor agonists (GLP-1RA) as subcutaneous injectables. The incretin hormone GLP-1 stimulates insulin secretion and inhibits glucagon secretion in a dose dependent manner.

DPP-4 inhibitors elevate endogenous GLP-1 concentrations by retarding the enzymatic degradation of GLP-1. They are most widely used as add-on insulinotropic oral medication to metformin, when a metformin monotherapy is not sufficient. In contrast to sulfonylureas, DPP-4 inhibitors have no intrinsic hypoglycaemia risk and they are body weight neutral. In cardiovascular (cv) safety studies, they have shown non-inferiority regarding a combined MACE primary endpoint compared to classical standard therapy[1-4]. In the recent cv safety study CARMELINA with linagliptin, this DPP-4 inhibitor also demonstrated safety in a study cohort with a high percentage of patients with an impaired renal function with a mean baseline eGFR below 60 ml/min and macroalbuminuria (appr. 40% of patients enrolled)[4].

GLP-1RA have pharmacological actions in addition to the stimulation of insulin secretion and the inhibition of glucagon secretion. They lower systolic blood pressure and allow body weight loss. The long acting injectable GLP-1RA albiglutide, dulaglutide, liraglutide and semaglutide have demonstrated superiority compared to standard therapy in cv safety studies regarding the primary MACE endpoint[5-8].

These data have led to a change in the recommendations for the treatment of patients with type 2 diabetes. The above mentioned GLP-1RA should be used in patients with type 2 diabetes and preexisting atherosclerotic cv disease as add on to metformin early on in order to reduce cv risk – independent of the HbA1c[9,10]. Likewise, GLP-1RA are now the injectables to be used primarily and before insulin therapy in the treatment of type 2 diabetes unless a severly deranged metabolic situation requires insulin or contraindications for GLP-1RA are present[9,10].

Regarding novel developments in the field of incretin based therapies, an oral formulation of semaglutide using SNAC as an en-

hancer to locally neutralize the gastric pH and to allow absorption of the peptide semaglutide into the circulation is far advanced in clinical development and has been tested in phase III studies with the acronym PIONEER[11].

Furthermore, dual- and triple incretin/glucagon agonists are in development, the dual GIP/GLP-1 agonist tirzepatide (compound LY3298176) is in the phase III clinical developmental programme demonstrating a stronger effect on HbA1c reduction and body weight reduction compared to dulaglutide[12].

In summary, DPP-4 inhibitors are safe and efficacious oral antidiabetic agents especially for patients with impaired renal function and in therapeutic settings where hypoglycaemia and weight gain need to be avoided. GLP-1RA are recommended for patients with preexisting atherosclerotic cv disease. New developments like dual- or triple agonists as well as oral semaglutide may widen the spectrum of available effective antidiabetic treatment.

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Pharmacogenetics of Type-2 Diabetes

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Currently, 7.5 million people in Germany are suffering from diabetes mellitus, more than 95% thereof from type-2 diabetes. The estimated costs for diabetes therapy reach about 16 billion € per year. Since prevalence data and costs will rise in the years to come, there is a clear need of cost-effective use of antidiabetic medication. Pharmacogenetic research aims at contributing to the reduction of therapy costs by allowing patient stratification and precision medicine.

Pharmacogenetics investigates the impact of genetic variation on treatment response and side effects. With respect to treatment response, the identification of gene variants associated with non-response and adverse response is paramount. The genes of interest are usually those related to pharmacokinetics and pharmacodynamics of a drug.

The pharmacogenetically best studied drug is metformin, the first-line drug in type-2 diabetes therapy. As metformin is not metabolized, pharmacogenetic investigation of metformin treatment focused on a manageable repertoire of pharmacokinetic genes. The organic cation transporter gene OCT1 was a major candidate gene because it harbors seven coding variants with reduced transport activity in vitro. Even though smaller studies provided evidence for some of these variants being associated with limited treatment response and metformin intolerance, the MetGen consortium including treatment studies with a cumulative sample size of about 8.000 subjects could not verify pharmacogenetic importance of these variants. Large collections of metformin treatment studies and the technological advances of the last 10 years finally allowed studying the impact of genetic variants on metformin response on a genome-wide scale (pharmacogenomics). These studies identified numerous non-coding variants in and around the ATM and SLC2A2 genes being associated with metformin treatment response. Unexpectedly, carriers of these variants revealed super-response to the drug limiting the usefulness of these findings for precision medicine. Larger study collections and consortia for pharmacogenomic investigation of other antidiabetic drugs are currently not available.

In close collaboration with pharmaceutical industry, we

could recently provide evidence for pharmacogenetic importance of pharmacodynamic gene variants in diabetes treatment using DPP4 and SGLT2 inhibitors. The pharmacodynamic target of SGLT2 inhibitors is the sodium/glucose transporter SGLT2 encoded by the SLC5A2 gene. SGLT2 is expressed in the proximal tubules of the kidney and is responsible for about 90% of renal glucose reabsorption. With rs3116150, we identified a common non-coding genetic variant in the SLC5A2 gene that is associated with elevated plasma glucose levels and increased systolic blood pressure already at baseline. Even though the treatment response was unaffected with respect to plasma glucose lowering, homozygous carriers of this variant revealed a substantial increase in systolic blood pressure (+8.9 mmHg) during 24 weeks of empagliflozin treatment. Thus, an estimated number of 40.000 T2D patients in Germany homozygous for this variant and treated with SGLT2 inhibitors are expected to experience blood pressure increase.

A pharmacodynamic target of DPP4 inhibitors and GLP1R agonists is TCF7L2, a transcription factor of pancreatic β-cells downstream of the GLP1R-cAMP-PKA signaling cascade which induces incretin receptor, prohormone convertase and insulin gene expression. We could demonstrate that the non-coding TCF7L2 variant rs7903146, the most important type-2 diabetes risk variant known to date, is associated with incretin resistance and impaired insulin secretion. Moreover, in a 24-week pharmacogenetic study, homozygous carriers of the variant revealed limited response to linagliptin treatment with respect to HbA1c lowering. Thus, about 400.000 T2D patients in Germany homozygous for this variant and treated with DPP4 inhibitors or GLP1R agonists are expected to experience limited treatment response. With Nor-1, encoded by the NR4A3 gene, we recently described a novel incretin-responsive transcription factor in β-cells which is likewise downstream of the GLP1R-cAMP-PKA axis and stimulates the expression of the insulin gene and a series of genes involved in the insulin secretory pathway. Additionally, we demonstrated that the non-coding variant rs12686676 in the NR4A3 gene locus interacts with TCF7L2 rs7903146 and enhances the insulin-secretion-impairing effect of TCF7L2 rs7903146. A similar synergism between the two SNPs was also observed with respect to incident type-2 diabetes in the EPIC-Potsdam study. Thus, we anticipate that subjects carrying both variants will have a markedly limited treatment response to DPP4 inhibitors and GLP1R agonists.

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Pancreatic fat accumulation, extracellular matrix expression and inflammation in healthy, pre-diabetic and diabetic individuals

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The last decade we studied many different fat depots in the body and focused on ectopic fat accumulation because there is increasing evidence that this fat is associated with the development of type 2 diabetes. Our group could demonstrate by magnetic resonance imaging (MRT) quantification in cooperation with the Dept. of Radiology that the amount of pancreatic fat is inversely associated with insulin secretion in subjects with prediabetes. It has been suggested that pancreatic fat reduction may help to improve beta-cell function during a lifestyle-intervention. This fat compartment seems to be a modulator of endocrine pancreas function. In our recent studies we characterized pancreatic adipose tissue both in vivo and in vitro. In histological sections we could detect pancreatic fat cell accumulation in the pancreatic parenchyma but we found significant inter-individual differences in the fat amount. Furthermore, we detected also many monocytes/macrophages infiltrating the parenchyma and even the islets.

In our in vitro studies we examined the crosstalk of human pancreatic fat cells with islets isolated from human pancreatic resections and characterized their pro-inflammatory potential. We found that islets augmented the inflammatory response of pre-adipocytes, the precursor cells of differentiated adipocytes. We showed also in vitro that plasma components of obese prediabetic humans, such as fatty acids (palmitate) and the hepatokine fetuin-A, stimulate the production of cytokines and chemoattractants in pancreatic fat cells which may trigger inflammation. Furthermore, extracellular matrix affects metabolic function in many tissues. Pancreatic β-cells function maybe also influenced by a specific microenvironment composed of ECM surrounding the islet. Thus, we examined also many extracellular matrix components, like collagens, elastin, fibronectin, laminin and growth factors, e.g. TGF-β. The extracellular matrix distribution and amount was examined histologically in human pancreatic resections and mRNA expression was studied in cell cultures. We observed that the amount of matrix proteins expressed by fat cells varies between non-, pre-, and diabetic individuals and that the crosstalk with the fatty liver by fetuin-A influences the extracellular matrix expression predominantly in fat cells from pre-diabetic subjects which might influence islet function additionally. However, also human islets express and secrete inflammatory factors and extracellular matrix proteins influencing fat cell function.

In summary these data show that pancreatic fat cells, immune cells, the surrounding extracellular matrix and the interactions with islets seem to play a pivotal role in diabetes and obesity predominantly in pre-diabetic patients with fatty liver.

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Diabetic retinopathy-through the eyes of a diabetologist

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Clincally, diabetic retinopathy (DRP) starts with the loss of capillary cells and subsequent occlusion of capillaries, first in the deep capillary layer, then extending to the other capillary layers and secondary abortive angiogenic response by the remaining capillaries which start forming microaneurysms. With progressive disease duration, increased vascular permeability and intraretinal angiogenesis ensue. The former leads to intraretinal fluid deposition and around the fovea to diabetic macular edema, while the latter, when the new vessels penetrate the inner limiting membrane, form proliferative retinopathy. Disease staging considers only vascular pathology while pathological changes are found in all cells of the neurovascular unit of the retina. Risk factors of the DRP development are: disease duration, glycemic levels, blood pressure, and type of diabetes (T1>T2). Older obese T2D patients have a 10% increased risk of any retinopathy, and albuminuria increases the risk of any retinopathy in T2D by 16%. Underlining the role of diabetic kidney disease in the complex pathogenesis of DRP, T2 persons with macroalbuminuria have a 2.8 fold increased risk of DME, a fact that is underestimated when DRP is not considered a complication of a systemic disease. Beyond the importance of regular screening during symptom-free early stages for the prevention of sight-threatening DRP, the detection of retinal lesions indicates a more than two-fold increased risk for future CVD events in both, T1 and T2 diabetes. Regular screening for retinopathy is therefore an important tool for CVD prediction.

Recent population based studies revealed that more than 7.5% of persons studied had diabetes of which more than one fourth were previously unknown. More than 20% of persons with diabetes had retinopathy, of which 5% had vision-threatening stages. This indicates that awereness of the disease and its complications is still insufficient.

Structural retinopathy including microaneurysms, exsudates, and hemorrhages is likely preceded by endothelial dysfunction of retinal vessels. Changes in the ratio between retinal arterioles and venoles – termed arterio-venous-ration (AVR) – and flickerlight-induced vasodilation are sensitive to metabolic and hemodynamic changes preceding overt diabetes. Studying a group of patients with

morbid obesity (WHO grade III), structural retinopathy was present in 3.4% of patients. Systolic blood pressure, increased intima-media thickness of the carotid artery and impaired venolar response to flicker-light were significant predictors of the development of structural retinopathy. Since mortality can also be predicted by impaired retinal vessel dilatation, it appears that retinal vessel dysfunction is a robust biomarker of CVD and mortality.

DRP is diagnosed by vascular changes, but diabetes strikes every cell of the neurovascular unit. Attempts to improve the prediction of vision-threatening stages by measure of retinal neuronal function have failed so far, but it needs to be noted that in some patients, diabetes induced cell damage can be measured first in retinal neurons, and then in the vasculature. This corresponds to the finding that simple clinical phenotyping identifies five subtypes of T2D, which were previously lumped together. Even more important, these phenotypes differ in their propensity to develop microvascular damage, the kidney being associated with subtypes of insulin resistance, while retinopathy is linked to the level of glycemia. That glycemia is a strong effector of retinal disease is further underlined by data showing that rapid euglycemic re-entry introduced by GLP-1 receptor agonists can sometimes deteriorate retinopathy. As the retina does not express the GLP-1 receptor to a great extent, and even looses the minimal expression in some ganglion cells during DRP progression, this effect is the consequence of systemic factors, not copied by other novel drugs such as SGLT-2 inhibitors or DPP4 inhibitors. The risk of euglycemic re-entry in T2D is almost exclusively explained by pre-existing retinopathy.

Therefore, diabetologists should use the eye as a window to the body's vasculature, and use fundus screening as a personalized biomarker of disease progression and general CVD risk.

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Diabetic nephropathy – an update

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Diabetic nephropathy is characterized by the development of albuminuria >300 mg/24 h and progressive deterioration of glomerular filtration rate in the setting of long-standing diabetes. Typically, patients are hypertensive and most importantly there is an increased risk for cardiovascular events and mortality. Besides its diagnostic role, recent studies have demonstrated that albuminuria is not only predictive of increased mortality risk in a linear manner but also of increased risk for end-stage renal disease. Furthermore, lowering of albuminuria has been shown to be associated with a protective effect underscoring the importance of albuminuria as biomarker for diabetic nephropathy. In addition to adequate treatment of hyperglycemia and blood pressure control, nephroprotection can be conferred by the use of renin-angiotensin-system blockers and is indicated by lowering of albuminuria. Currently, inhibitors of the sodium-glucose-transporter 2 (SGLT2) emerge as a new and additive treatment that has been shown to both prevent cardiovascular events and disease progression in patients with established diabetic nephropathy. Treatment with SGLT2 inhibitors on top of renin-angiotensin-system blockers further reduced albuminuria which can be explained by lowering of intraglomerular pressure. In addition to SGLT2 inhibitors, agonists of glucagon-like peptide 1 receptor have been shown to lower albuminuria as well and might have a nephroprotective potential, however, evidence from clinical studies with renal end points are lacking.

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Prevention of type 2 diabetes mellitus

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Introduction

Type 2 diabetes occurs in 7% of the US population and affects ~ 21 million individuals and is characterized by hyperglycemia, insulin resistance, and relative impairment in insulin secretion. Prediabetes is defined as an intermediate metabolic state between normoglycemia and diabetes and includes those with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Although the lifetime risk of type 2 diabetes is high, our ability to predict and prevent type 2 diabetes in the general population is limited. However, individuals at high risk, including those with prediabetes, are appropriate candidates for preventive interventions.

Goals of diabetes prevention

The goals of diabetes prevention include: 1. Delaying the onset of diabetes, 2. Preserving beta cell function and 3. Preventing or delaying microvascular complications and perhaps cardiovascular complications.

Lifestyle Intervention

Lifestyle intervension (combined diet and exercise aimed at weight loss and increasing activity levels) can improve glucose tolerance and prevent progression from prodiabetes to type 2 diabetes, as illustrated by meta-analyses of trials comparing exercise plus diet with standard therapy.

The strongest evidence for diabetes prevention comes from the Diabetes Prevention Program (DPP). The DPP demonstrated that an intensive lifestyle intervention could reduce the incidence of type 2 diabetes by 58% over 3 years. Follow-up of three large studies of lifestyle intervention for diabetes prevention has shown sustained reduction in the rate of conversion to type 2 diabetes: 43% reduction of 20 years in the Da Qing study, 43% reduction at 7 years in the Finnish Diabetes Prevention Study (DPS) and 34% reduction at 10 years in the US Diabetes Prevention Program Outcomes Study (DPPOS).

Pharmacologic Interventions

Pharmacology agents including metformin, a-glucoside inhibitors, orlistat, glucagon-like peptide 1 (GLP-1) receptor agonists, thiazolidinediones and vitamin D, have each been shown to decrease incident diabetes to various degrees in those with prediabetes in research studies, though none are appoved by the FDA and EMA specifically for diabetes prevention.

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Low calorie diet in diabetes mellitus type 2

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There is substantial evidence indicating that weight loss is highly effective in managing glycemic control and cardiometabolic health in type 2 diabetes (DM2). Therefore, medical nutrition therapy (MNT) and comprehensive diabetes self-management education and support (DSMES) that include an overall healthy eating plan in a format that results in an energy deficit, as well as a collaborative effort to achieve weight loss in people with type 2 diabetes who are overweight/obese, are recommended. In DM2, 5% weight loss (WL) is recommended to achieve clinical benefit and the benefits are progressive. The goal for optimal outcomes (e.g. diabetes remission) is 15% or more WL when needed and can be feasibly and safely accomplished. Eating plans that create an energy deficit and are customized to fit the person's preferences and resources can help with long-term sustainment and are the cornerstone of weight loss therapy.

15% or more WL is achieved with low calorie diets. The term "low calorie diets" includes low calorie diets (LCDs), very low calorie diets (VLCDs) and intermittent fasting (IF). The key points of these diets are that they vary depending on the type and amount of carbohydrate, protein and fat consumed to meet the daily caloric intake goals. Diets of equal caloric intake result in similar weight loss regardless of the macronutrient content. Also, the metabolic status of the patient based on lipid profiles, renal and liver function is the main determinant for the macronutrient composition of the diet.

LCDs are defined as diets with caloric deficit 500-800 Kcal per day from energy demand (ED). They usually use conventional food but meal replacements can be used as well.

VLCDs are defined as diets limiting energy intake to 450–800 kcal per day, while providing at least 50 g of high-quality protein and amino acids, essential fatty acids and daily requirements of trace elements, vitamins and minerals. They are recommended only in the obese [body mass index (BMI) $\geq$30 kg/m^2] or in individuals with BMI >27 kg/m^2 plus one or more co-morbidities. Generally, they involve an intensive phase (three meal replacements) usually lasting 8-16 weeks. In addition, two cups of salad or low-starch vegetables are eaten to provide fiber to lessen hunger and reduce constipation. A tablespoon of oil or butter and 2 liters of water or calorie free beverages are also consumed to prevent gallstones. Subsequently,

reintroduction of conventional food (12-14 weeks) in the diet and then followed by a weight stabilization program.

IF has recently gained popularity as a mean of reducing body weight and improving metabolic status. An important feature of IF schedules is that all meals are consumed during a strictly defined window of time and followed by fasting. Such fasting is achieved by ingesting little to no food or caloric drinks for periods that typically range from 16 to 24 hours, e.g., as the prolongation of the physiological overnight fast. Thus, the IF method does not describe which nutrient types are allowed, assuming only that the person eats a balanced diet and conforms to the rules of healthy eating. Because the time span of the "feeding window" is short, the overall calorie intake is lower than if the food intake time was unlimited. Different regimens of IF have been employed in daily practice and clinical trials. The most popular is alternate day fasting (ADF), which involves "fast days" alternating with "feed days" (ad libitum food consumption), typically carried out for weeks to months.

There are some absolute contraindications to the use of very-low-calorie diets such as, BMI <25 kg/m^2, pregnancy/lactation, clinical eating disorder, major psychiatric illness, severe systemic or organ disease, e.g.: recent myocardial infarct/angina/stroke, major dysrhythmia, severe renal/hepatic disease, malignancy, wasting disorders, e.g. Cushing's syndrome. Thus, there are some relative contraindications such as, age >65 years, child <16-18 years, type 1 DM, gout, cholelithiasis.

Effects of VLCDs and IF on plasma glucose levels occur rapidly, a decrease in mean glucose levels is seen within days and reaching near nadir after 1-2 weeks. Calorie restriction leads to glycogen depletion in muscle and liver. Thus, restriction of carbohydrate leads to lipolysis and the formation of ketone bodies by the liver. Together, these lead to reductions in hepatic glucose output via inhibition of gluconeogenesis and reduced glycogenolysis. High protein stimulates insulin secretion and increases satiety. Circulating ketone bodies probably contribute to tolerability of the diet by suppressing appetite in the hypothalamus. Weight loss and diminution of fat depots in the liver, muscle and peri-visceral space lead to reductions in insulin resistance. Improved insulin sensitivity, dynamic insulin secretion and reduced hepatic glucose output lead to reductions in blood glucose levels.

Recent studies showed that in the first 10 years of type 2 diabetes, negative calorie balance rapidly normalizes liver fat content, hepatic glucose production and fasting plasma glucose; and if the negative calorie balance is sustained, intra-pancreatic fat content and insulin secretion also normalize and may lead to diabetes remission.

The paucity of controlled, large-scale research trials makes it difficult to prescribe LCDs or IF as reliable, routine methods for safe and successful, stable weight loss. VLCDs are considered safe and effective when used by appropriately selected individuals under careful medical supervision.

Weight regain after dietary interventions is a common occurrence and further exploration of weight loss and weight maintenance could also lead to identification of the best active ingredients for optimum weight loss and its maintenance in the future.

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Exercise in Type 1 Diabetes

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Introduction

It is well established that regular exercise is beneficial and improves cardiovascular profile both in nondiabetic and people with type 1 diabetes. Regular exercise in adults with type 1 diabetes, can improve health and wellbeing, helps to achieve better glycaemic control, improves lipid profile and blood pressure control, decreases BMI. However, several additional barriers to exercise can exist for a person with diabetes, including fear of hypoglycaemia, loss of glycaemic control, and inadequate knowledge around exercise management. Adequate education about exercise as well as several adjustments have to be made in insulin regimens and carbohydrate intake before and after recovery from exercise in order to avoid hypoglycemia. Recommendations in diabetes, including those living with type 1 diabetes, 150 min of physical activity is recommended each week, with no more than two consecutive days of no physical activity. Resistance exercise is recommended also.

According to the American Diabetes Association Physical Activity Guidelines, for all adults living with diabetes recommended two to three times a week[1].

Physiology of physical activity and exercise

Modes of exercise

Exercise is generally classified as aerobic or anaerobic, depending on the predominant energy systems used to support the activity, although most exercise activities include a combination of energy systems. Aerobic exercise (e.g., walking, cycling, jogging, and swimming) involves repeated and continuous movement of large muscle groups that rely primarily on aerobic energy-producing systems. Resistance (strength) training is a type of exercise using free weights, weight machines, bodyweight, or elastic resistance bands that rely primarily on anaerobic energy-producing systems. High intensity interval training involves alternation between brief periods of vigorous exercise and recovery at low to moderate intensity (e.g., from 20 s to 4 min intervals of exercise and rest, for up to ten cycles). Both aerobic and anaerobic activities are recommended for most people living with diabetes.

Neuroendocrine and metabolic responses to exercise

In a nondiabetic individual, in almost all forms of exercise, regardless of the intensity or duration, blood glucose concentrations are within a narrow range (70-110 mg/dL). During aerobic exercise, insulin secretion decreases and glucagon secretion increases in the portal vein in order to stimulate the release of glucose from the liver to match the rate of glucose uptake into the working muscles[2]. Although the main determinant of glucose production during aerobic exercise is an increase in glucagon concentrations, other counterregulatory hormones also have a supportive role. A longer duration of exercise leads to glycogen depletion in the muscle, and energy fuel depends on lipid oxidation and glucose derived from plasma[3].

In type 1 diabetes, the glycaemic responses to exercise are influenced by the location of insulin delivery, the amount of insulin in the circulation, the blood glucose concentration before exercise, the composition of the last meal or snack, as well as the intensity and duration of the activity[4]. During aerobic exercise, blood glucose concentrations fall in most individuals with type 1 diabetes, because insulin concentrations cannot be decreased rapidly enough at the start of the activity and remain elevated in the systemic circulation. Increased insulin concentrations in the circulation during exercise promote increased glucose disposal relative to hepatic glucose production[5]. Hypoglycaemia develops in most patients within about 45 min of starting aerobic exercise. Individuals with type 1 diabetes typically require an increased carbohydrate intake or an insulin dose reduction, or both, before commencing aerobic exercise[6,7]. Low insulin concentrations due to aggressive reductions in insulin administration or a skipped insulin dose can cause hyperglycaemia before and during aerobic exercise, and even mild activity could lead to development of ketosis[8]. In brief and intense anaerobic exercise (e.g., sprinting, weight lifting, and some competitive sports), or during high intensity interval training, glucose concentrations typically rise[9].

Glucose uptake into muscle decreases immediately after aerobic exercise, but overall glucose disposal remains elevated for several hours in recovery from exercise to help replenish glycogen stores[10]. The risk of hypoglycaemia is elevated for at least 24 h in recovery from exercise, with the greatest risk of nocturnal hypoglycaemia occurring after afternoon activity[11]. Weight lifting, sprinting, and intense aerobic exercise can promote an increase in glycaemia that could last for hours in recovery. Although a conservative insulin correction after exercise might be prudent in some situations, overcorrection with insulin can cause severe nocturnal hypoglycaemia[12].

Contraindications for exercise

Elevated Ketones

Monitoring of blood or urine ketones is necessary before exercise. The cause of elevated ketones should be identified and be corrected appropriately by carbohydrate and insulin administration.

Recent Hypoglycemia

Severe hypoglycemia within the previous 24 hours is a contraindication to exercise because of a more serious episode during exercise. Even a single episode of mild hypoglycemia within 24 hours before exercise may disrupt counterregulatory responses and symptom awareness during exercise[13]. On the other hand a single bout of exercise may decrease counterregulatory responses during subsequent hypoglycaemia[14].

Diabetes complications and Exercise

Vigorous exercise, activities involving lifting of heavy weights, and competitive endurance events are contraindicated, in patients with long standing type 1 diabetes or with high HbA1c concentrations particularly if the patient has unstable proliferative retinopathy, severe autonomic dysfunction, or renal failure[15].

Clinical Treatment

Clinical management strategies depend on the type and duration of exercise. Implementation of the strategies take into account insulin dosage adjustment, carbohydrate intake, blood glucose monitoring or CGM, and insulin sensitivity of the subject. Generally, sustained aerobic exercise requires greater reductions in insulin dose and a higher carbohydrate intake than a short-term high intensity interval training session. By contrast, brief anaerobic exercise could require increased insulin delivery,

recommended to be given in early recovery rather than before exercise to avoid hypoglycaemia[16].

Continuous subcutaneous insulin infusion offers more flexibility to modify basal infusion delivery and obtain a faster effect. Suspension of basal insulin infusion at the onset of 60 min exercise reduces the risk of hypoglycaemia during the activity, but it could increase the risk of hyperglycaemia after exercise[17]. A basal rate reduction, rather than suspension, is recommended 60-90 min before the start of exercise. An 80% basal reduction at the onset of exercise has been shown more effective in preventing hyperglycaemia after exercise than does basal insulin suspension, and is associated with a reduced risk of hypoglycaemia both during and after the activity[18]. To limit the risk of compromised glycaemic control and ketosis, a time limit of less than 2 h for pump suspension is recommended[19].

Latest advances in technology with continuous glucose monitoring, and continuous subcutaneous insulin infusion help patients with type 1 diabetes to perform exercise with safety. Real time CGM may alert the patient about hypo- or hyperglycaemia while they exercise or perform sports. Threshold suspension of insulin delivery in continuous subcutaneous insulin infusion could offer additional protection against exercise-associated hypoglycaemia[20]. The development of the artificial pancreas for exercise remains the ultimate goal[21].

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Running for a future without diabetes?

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Physical exercise is a commonly accepted strategy to increase the healthspan in our ageing societies and to prevent metabolic diseases such as diabetes. However, not all individuals profit to the same extent. Subjects who failed to improve in glycemic control were observed in almost all of the populations studied, and this failure is at least partially independent of other investigated endpoints, e.g. cardiorespiratory fitness, blood pressure, lipid profile, and body weight. These subjects were described as non-responders in glycemic control. However, this definition can be misleading as higher exercise loads have been shown to overcome the failure to respond in fitness parameters. Whether this can be applied to pre-diabetic subjects to improve the metabolic response is under debate. On a molecular level, improvement in glycemic control is associated with increased abundance of mitochondrial regulators and enzymes in the trained skeletal muscle, and increase in mitochondrial respiration. Mechanisms interfering with the metabolic benefit of exercise are widely unclear.

Results of an exercise intervention study in Tübingen indicate a crosstalk of inflammatory pathways with the metabolic response after training. 20 middle-aged individuals (untrained, high risk for type 2 diabetes) performed 8 weeks of cycling and walking training at 80% individual V_{O2} peak. In this structured and supervised exercise intervention study, all participants were able to improve their fitness, but 40% did not increase their insulin sensitivity. In muscle biopsies taken before and after the training period, we found a reduced up-regulation of genes pivotal for glucose and fat utilization in skeletal muscle tissue of non-responders, as well as increased transcripts pointing to local inflammation, among others TGFβ (transforming growth factor beta). In human skeletal muscle cells, TGFβ1 downregulates the abundance of important genes in energy metabolism (PPARGC1A, PRKAA2, TFAM, HADHA, CPT1B), inhibits insulin signal transduction and suppresses myotube differentiation. The data suggest that a dysregulated adaptive process in skeletal muscle leads to increased TGFβ activity and can attenuate the improvement in glycemic control. In ongoing research, the downstream effectors of TGFβ as regulator of metabolic adaptations are studied.

The metabolic dysregulations in glucose and lipid metabolism have been associated with a reduced efficiency of exercise to improve glycemic control. Comparison of the acute response of age-, BMI-, and fitness-matched type 2 diabetic subjects and healthy controls to one bout of aerobic exercise did not indicate reduced metabolic flexibility or impairment of transcriptional response.

Moreover, since the increase in mitochondrial respiration in skeletal muscle can only partly explain the improvement of glycemic control, the involvement of additional non-muscle adaptions is discussed.

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Enteric microbiome and Diabetes mellitus

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The complex relationship between diabetes, obesity and gut microbiota is being released with emerging evidence. Investigation of human microbiome is the most rapidly expanding field in biomedicine. Enteric microbes are key players in the management of glucose homeostasis in humans. There is unmet need to clear all related mechanisms so as to develop new therapeutic approaches for people with diabetes mellitus.

The term "microbiome" refers to the totality of microbes colonizing humans and their genes[1]. The gastrointestinal tract harbors about 100 trillion microbes including archaea, bacteria protozoans, viruses and fungi. *Formicates* such as Lactobacillus, Ruminococcus and Clostridium species, as well as *Bacteroidetes* and *Actinobacteria* account for the largest proportion of microbiota.

The enteric microbiome achieves very important physiological functions: protection against pathogens, synthesis of vitamins, immune system development, promotion of intestinal angiogenesis and fat storage, digestion of complex carbohydrates and SCFA production[2]. The gut-hypothalamus axis is influenced by microbes through hormones and neurotransmitter release in order to regulate food intake and energy balance[3].

Carbohydrates are the primary sources of energy for both the human host and their microbes. Humans lack enzymes for digestion of complex carbs including cellulose, xylans, resistant starch and inulin. Microbiome encode enzymes required for indigested carbohydrates fermentation. The latter harvests energy for microbial growth and produces monosaccharides and short-chain fatty acids (SCFAs), which act as ligands for G protein-coupled receptors GP41 and GP43 which are abundant in adipose tissue, intestinal epithelial and immune cells. SCFAs have significant effects on the gut wall health as a source of energy, anti-inflammation agents, vasodilators, promotility agents and wound healing components. Butyrate is principally used as an energy source for enterocytes, whereas acetate and propionate are used by the liver for lipogenesis and glyconeogenesis.

The gastrointestinal tract microbiome is affected by host nutrition, environment and host genetics and thus it develops obesity related metabolic disorders such as diabetes mellitus. The term "dysbiosis" refers to pathological alterations in the gut microbiota and is

generally induced by high fat diet[4]. Dysbiosis enhances energy harvest through a change in the Bacteroidetes/Firmicutes ratio. Altered microbial composition –characterized by poor species richness and diversity– provokes distorted SCFAs profile and consequently less expression of G-protein receptors leading to poor energy homeostasis, obesity, insulin resistance and type 2 diabetes mellitus (T2DM).

Microbiome-triggered chronic low-grade inflammation is another important causal factor for T2DM. Symbiosis impairs intestinal wall integrity and high mucosal permeability causes translocation of endotoxins (lipopolysaccharides – LPS) from the lumen to the systemic circulation. End toxemia leads to low-grade inflammation, autoimmunity and oxidative stress that probably induce beta cell destruction and insulin resistance. In terms of autoimmunity, LPS stimulates innate immune responses by activating CD14, nucleotide oligomerization domain (NOD) and toll-like receptor 4 (TLR4) at the surface of dendritic cells and macrophages[5].

Type 1 diabetes mellitus (T1DM) is probably caused by a chronic inflammatory disease of the gastrointestinal tract in hereditary prone individuals, leading to autoimmune destruction of β-islet cells[6]. The disease is associated with microbiome symbiosis. A higher proportion of *Actinobacteria, Bacteroidetes* and *Proteobacteria* is distinctive of T1DM[7]. A second possible mechanism for the enteric microbiota to induce T1DM is that gut leakiness, endotoxemia and low-grade inflammation initiates immune deregulation[8]. Oxidative stress might be a third pathogenic factor caused by microbial dysbiosis[9]. It is still uncertain if these microbiome-related metabolic oxidative stress, autoimmunity and low-grade inflammation act independently or together.

Several studies concerning the role of bile acids, GABA and endocannabinoid system in the pathogenesis of T2DM have been so far published. Sex hormones observed to affect autoimmunity in early life and subsequently cause T1DM. But these studies were conducted with mice and not with humans, so as much work has to be done furthermore.

Microbial dysbiosis is associated with gestational diabetes mellitus due to impaired intestinal barrier and thus endotoxemia.

Metformin is one of the most prescribed oral antidiabetics. Although this regimen does not administer to modify gut microbiota, there is a growing evidence that some effects are attributed to changes in microbiome composition. Metformin induces a higher abundance of the mucin degrading bacterium *Akkermansia muciniphilla* leading to gut barrier be more resilient. In humans, metformin seems to reduce intestinal lipid absorption and LPS-triggered local inflammation as an effect of modified enteric microbiome[10].

Metabolic surgery, specifically RYGB markedly altered the composition of the distal gut microbiota in mice, 1 week after surgery. A decrease in body weight, improved insulin sensitivity and reduced fasting triglyceride levels were documented. RYGB leads to a specific spectrum of microbiota per se[11]. These findings need to be corroborated in humans.

Administration of probiotics has a beneficial role in the management of T2DM, since they significantly decreased FPG and HbA1c in diabetic patients[12]. Probiotics also showed anti-inflammatory and anti-oxidative effects in diabetic patients. Findings still imply a need for well-designed clinical trials. Probiotic approaches in T1DM aim more on the modulation of the diabetes risk in stages with HLA−susceptibility or antibody formation than in manifest disease. Lactobacillus species negatively correlated with T1DM development. Diabetes-rone rats administered L. johnsonii developed T1DM at a protracted rate[13]. Further proposed targets for a probiotic therapy in T2DM include the endocannabinoid system and GABA.

Many animal experiments where gut microbiome was transferred between individuals have already been published. In humans with metabolic syndrome, only one study –designed to treat– has been so far reported[14]. Improvement of peripheral insulin sensitivity and increase of the levels of butyrate-producing microbiota, such as *Roseburia intestinalis*, were noted.

For a medical doctor, the rapidly evolving field of metagenomics, is impossible to be overlooked. Although a different microbe composition in diabetic patients prevails, the patient numbers are often low, results are contradictory and methodology is different. We still lack knowledge of a normal gut microbiota. This may vary in different geographical regions, depend on different nutritional habits, gender, age, etc.

Scientific approaches focus on bacteria, while other microbes are still neglected. In T1DM, viruses

particularly coxsackie viruses infect human pancreatic β-cells. Other viruses such as rotavirus or rubella virus have been discussed in the pathogenesis of T1DM. So far, it is unknown whether fecal microbiota transplantation from a donor with a desired phenotype may not put the recipient at risk for other diseases.

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Hellenic Diabetological Chronicles 32, 3: 145-147, 2019

Gestational diabetes mellitus

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There is a huge scientific interest with a lot of publications in the last decade dealing with the hyperglycemia in pregnancy because of increased risk for the mother and fetus accompanying this condition. The hyperglycemia in pregnancy can be classified 1. as diabetes in pregnancy and 2. as gestational diabetes mellitus (FIGO 2015). The last few years is made clear that the excellent metabolic control during pregnancy leads to less perinatal and future complications for mother and fetus. The diabetes in pregnancy can be divided as diabetes diagnosed before pregnancy (Type 1 and Type 2) and as diabetes diagnosed for the first time during pregnancy (Type 1 and Type 2). The gestational diabetes mellitus was earlier defined as any glucose intolerance beginning or first diagnosed during pregnancy. The current definition, based on recent studies, includes the hyperglycemia state diagnosed in the second and more often in the third trimester of pregnancy which does not fulfill the criteria for overt, classical diabetes but coincides with the state of prodiabetes.

In every pregnancy there is a state of insulin resistance due to increased levels of hormones counteracting the insulin action (human chorionic goanadotropin from synciotblasts and later human placental lactogen, prolactin, progesterone and estradiol). The levels of these hormones become higher with the progression of the pregnancy leading to further increase of insulin resistance. If the maternal pancreas can compensate with increased insulin production the glucose metabolism remains normal during the whole pregnancy but, if there is also an insulin secretory(b-cell) defect, the insulin production can not increase appropriately and hyperglycemia evolves. In normal pregnancies during the OGTT, according to many studies, the fasting glucose is about 71±8 mg/dl, the one-hour PP value is 109±13 and the 2hours PP is 99±10 mg/dl. If we add 1SD to these values the 1h PP the suggested target is 122 and the 2h PP is 110 mg/dl respectively. There was a lot of disagreement among the various authors and diabetes associations and many modifications in the last 55 years about which OGTT should be used to define the gestational diabetes and predict better the risk for adverse pregnancy outcome. A 1,2 and 3hours OGTT have been used with the administration of 50, 75 or 100 gr of glucose. In 2008 the HAPO (Hyperglycemia and Adverse Pregnancy Outcome)

study was published. 25.000 pregnancies with mild glucose intolerance were studied with a 2h, 0' 1 and 2h glucose values, 75 gr OGTT performed between 24 and 32 gestational weeks. Women with FPG>105 and 2h PP>200 mg/dl were excluded from the study. The primary end points were BW>90th percentile, umbilical C-peptide>90th percentile, neonatal clinical hypoglycemia and caesarean section percentage. There was an absolute linear correlation between the pregnant women glucose values with these primary end points at values lower than those seen in classical diabetes. Similar results were observed in the ACHOIS and MFMU (Maternal and Fetal Pregnancy Units, trials. According to these trials in 2010 the International Association of Diabetes and Pregnancy Study Groups (IADPSG) Recommendations of Hyperglycemia in Pregmancy (Consensus) were published with gestational diabetes diagnosed if the following values were met or exceeded: Fasting 92 mg/dl or 5,1 mmol/l, one hour 180 mg/dl or 10 mmol/L and 2 hours 153 mg/dL or 8,5 mmol/L in an OGTT with 75 g of glucose at 24-28 pregnancy weeks (one-step strategy). One abnormal value is sufficient for the diagnosis of GDM to be made. The two-steps strategy can also be used with 50 g of glucose (non fasting) given as screening test and if the one hour glucose value is >140 mg/dL or 7,8 mg/L the 3-hours OGTT with 100g of glucose (fasting) is performed. The diagnosis of gestational diabetes is made if 2 of the 4 glucose values in fasting, 60', 120' and 180' meet or exceed the following: Fasting 92 mg/dL or 5,1 mmol/L, 1h 180 mg/dL or 10 mmol/L, 2h 155 mg/dL or 8,6 mmol/L and 3h 140 mg/dL or 1,8 mmol/L. (ADA 2016). The Hellenic Diabetes Association recommends that all the pregnant women must be screened fasting in the first visit and if the value is <92 perform a 2hs OGTT with 75 g glucose at 24-28 pregnancy week. If the glucose value is >92 and <126 there is gestational diabetes and if it is ≥126 or the 2h PP is ≥ 200 mg/dL there is overt type 2 DM.

Risk factors for gestational diabetes are among others history of IGT or GDM, age > 25 years, BMI>30 with excessive weight gain, family history of DM, history of POS or pregnancy with bad outcome, presence of metabolic syndrome, multiple pregnancy and some nationalities. Some of these are modifiable and some not modifiable. The relative risk of neonatal birth weight above the 90th percentile is 5,35 if there is GDM and the mother is obese compared with normal glucose tolerance and normal mother's weight. The glycemic targets during pregnancy in order to prevent mother and fetal complications according to experts' opinion in pregnant with GDM are: preprandial (premeal) ≤90 mg/d (5 mmol/L)l, 1-hour postprandial ≤ 120 mg/d (6,7 mmol/L)l and HbA1c ≤ 5%.The same targets are valid for women with preexisting type 1 or type 2 DM with the exception of HBA1c which must be≤6%).

75% of women with GDM can be controlled with life style modifications alone (diet and exercise). The diet must not contain less than 1600-1800 Kcal/24 h. The carbohydrates must be≈35-45% of the total caloric intake (no easily absorbable sugars), the protein 20-25% and the fats 30-40%. The meals must be small and frequent to avoid ketosis and in obese women medium caloric restriction (25 Kcal/Kg/day) is recommended. The exercise sessions must be either 30 min of aerobic exercise (e.g. brisk walking) in 24hs in exercise capable women or upper limbs exercise in sitting position lasting at least 10 min (after meals). If the life style changes are not sufficient for adequate glucose control drug therapy must be initiated. Insulin, glibencamide (glyburid) and metformin are safe and effective therapy for achieving desirable glycemic control. However there is no long term sufficient evidence for oral antidiabetic therapy and insulin is preferred. According to a metaanalysis glibenclamide is clearly inferior both to metformin and insulin. Metformin does not seem to increase risk for fetal malformations while half of the patients on metformin will finally require insulin. Glibenclamide caused more neonatal ICU admissions, more cases with respiratory distress, hypoglycemia, birth injury and large for gestational age infants compared with insulin. Insulin must be initiated if FBG is >95 mg/dL, 1-hour postprandial >140 or there is fetal macrosomia in ultrasound (abdominal circumference >75th percentile). Insulins considered safe in pregnancy are these with intermediate duration of action NPH and levemir, the human regular insulin and the preferred rapid-acting analogs aspart and lispro (category B). Insulin glargine although frequently prescribed in pregnancy has not been definitely established as safe (category C).

Women with GDM must be followed every two

weeks both by the obstetrician and the diabetes specialist, must have an initial HBA1c in order to exclude preexisting DM, must measure their blood glucose 4-6 times daily (before and 1-hour after meals) and have an ultrasound every 2-3 weeks. Continuous glucose monitoring with CGMS in GDM has shown benefits in many cases. This helps when there is inability to achieve the desired glycemic control with SMBG alone as it identifies undetected glucose excursions. It can lead to reduced birth weight and decreased risk for infant macrosomia by improving the glycemic control in the third trimester. The recommended mothers' weight gain during pregnancy is related to pregestational BMI. A woman with pregestational BMI>30 must not gain more than 5-9 Kg while one with BMI <18 is allowed to gain 12-18 Kg.

The complications in mothers with GDM include preeclampsia, hypertension in pregnancy, mother's birth trauma and increased risk for caesarean section. The long term mother's complications include the increased risk for future development of DM type 2 (X5 in 5 years, X10 in 10 years) and increased risk for future cardiovascular disease. It is recommended that the mother is monitored for dysglycemia at regular intervals after delivery: 1-3 days – FBG, 2-3 months – OGTT, 1year – OGTT, every year – FBG, every 3 years and before next pregnancy – OGTT.

The fetal complications in GDM include sudden intrauterine (after 38wk) and perinatal death, macrosomia, fetal trauma or asphyxia, shoulder dystocia, neonate respiratory distress syndrome (RDS), polyhyramnio, fetal hypertrophic cardiomyopathy and metabolic abnormalities as hypoglycemia, jaundice, polycythemia and hypocalcemia. Long-term offspring's complications include increased risk for obesity, prediabetes and type 2 diabetes and both systolic and diastolic hypertension during their adolescence and adulthood. The GDM is no indication for caesarean section by itself, lactation is desirable while women on insulin usually don't need it during labor and is usually stopped after this. Lactating women even for 6-9 weeks after delivery had lower frequency of prediabetes and type 2 diabetes compared with the non lactating.

It is concluded that there is a need for search for preexisting DM from the first visit, the prevalence of GDM is increased due to world obesity pandemic, the GDM is pathophysiologically correlated to increased insulin resistance, there is a direct and linear correlation of hyperglycemia with adverse perinatal outcome, GDM must be searched and treated vigorously, life style and insulin are the appropriate treatment options and the women with GDM are at increased risk for future development of DM type 2 and CVD.

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Management of Diabetes Mellitus type 2 during hospitalization

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Diabetes Mellitus (DM) is a metabolic disorder that affects more than 415 million people worldwide. That means that in every 11 adults 1 has diabetes. In the hospital setting DM is more frequent affecting 1 in 4 patients but apart from that, there is also a number of patients with hyperglycemia without known prior history of diabetes. In these patients 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 caused by increased levels of counterregulatory hormones and inflammatory cytokines.

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 are no randomized trials regarding glycemic control in patients in the general medical ward. There is data from patients in the intensive care unit (ICU) but without strong evidence to demonstrate that tight glycemic control (blood glucose target level of 80-110 mg/dl) in inpatients improves outcomes. In contrast, patients who experience hypoglycemia during a hospitalization tend to have a longer length of stay. It seems that 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, a blood glucose (BG) level 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. Therefore treatment should be applied in case BG levels rise above 180 mg/dl. A tighter 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 of the lack of safety and efficacy studies in the inpatient setting. Metformin and SGLT-2 inhibitors should be used with caution because of the risk of lactic acidosis and diabetic ketoacidosis respectively. However, increasing evidence indicates that treatment with GlP-1R agonists and 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.

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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New insights in NAFLD and diabetic nephropathy in patients with diabetes mellitus type 2

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Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of fat in the liver of people who take minimal or no alcohol. It incorporates a spectrum of conditions ranging from simple steatosis to steatohepatitis, advanced fibrosis and cirrhosis[1].

NAFLD is emerging as the most common cause of chronic liver disease worldwide. The global prevalence of NAFLD is believed to be as high as 25%[1]. In Europe, the prevalence in the general population has been shown to be between 2% and 44%[1,2]. The prevalence of NAFLD is observed to be much higher (24%-69.5%) in patients with diabetes mellitus[3-5]. The variation in prevalence estimates relates to the methods used in the diagnosis of NAFLD. Chronic Kidney Disease (CKD) is a global public health problem, affecting >25% of individuals above the age of 65 years in Western adult populations[6,7].

The US Renal Data System reports that over 670.000 people in the USA received some form of renal replacement therapy (RRT) at the end of 2014, and this number is predicted to reach 2.2 million by 2030[7]. The association between NAFLD, CKD and cardiovascular disease (CVD) has been of increasing interest in recent years. Despite being regarded as the hepatic component of the metabolic syndrome, which includes diabetes, hypertension and obesity, NAFLD has been shown to be an independent risk factor associated with CVD[8-10]. In patients with NAFLD, a high incidence and prevalence of CKD have been observed and a strong association between the two conditions has been reported[11-15]. CKD in itself is an independent risk factor for CVDs, and the majority of patients do not reach end-stage renal disease (ESRD) due to the high risk of mortality associated with cardiovascular events[16-18]. The presence of NAFLD in advanced CKD patients is likely to compound their cardiovascular risk.

All recent studies were not conducted to gain insight into the prevalence of NAFLD in advanced CKD and to investigate whether NAFLD had any influence on three primary outcomes:

i) all-cause mortality

ii) non-fatal cardiovascular events (NFCVEs) and

iii) rate of progression of CKD in a large cohort of non-dialysis CKD patients.

The most recent observational study has given further insights into the association of NAFLD with CVD, CKD progression and mortality in patients with CKD. The prevalence of NAFLD was 17.9% in their secondary care CKD cohort.

Prevalence was much higher (30.7%) in diabetics[19]. These data are similar to the reported prevalence of NAFLD in other international populations[2,20,21]. The prevalence was almost the same as that reported in a large US general population survey (19%) that used ultrasound in the diagnosis of NAFLD[22]. Although a very high prevalence (85.5%) of NAFLD as determined by fibroscan has been reported in a CKD cohort, this was a small study, involving only 62 patients[23]. The wide variation in prevalence estimates depicts the methods used in the diagnosis of NAFLD.

In overall CKD populations, patients with NAFLD were more likely to have components of the metabolic syndrome including hypertension, diabetes, hyperlipidaemia and high body mass index, lending support for the association of NAFLD with the metabolic syndrome[24-26]. The total cholesterol HDL ratio was significantly greater in the NAFLD group, which also reinforces the link to the metabolic syndrome[27]. The United States National Health and Nutrition Examination Survey (NHANES-III) study also showed similar all-cause mortality of all age groups in participants with and without NAFLD[28,29].

Recent research has shown that liver fat related to hypovitaminosis D may increase the risk of hypertension, vascular disease, diabetes mellitus, obesity and Metabolic Syndrome[30]. Several pro-inflammatory and oxidative stress mechanisms have been postulated to explain the relationship between these two conditions [fig. 1].

This association of NAFLD with CVD has been consistently shown in meta-analyses and systematic reviews of the general population[31,32]. NAFLD is closely linked to obesity[33,34]. Several potential pathophysiological mechanisms, including the role of pro-oxidant, proinflammatory and procoagulant mediators, have been postulated to be responsible for the increased CVD risk in NAFLD patients[35-38].

We have previously studied how fast and easily mobilisable is hepatic fat with proper diet and organized lifestyle intervention within 4-8 weeks. In 62 out of 100 diabetics with marked hepatic fat, 20 minutes walking a day and Mediterranean diet (fish, vegetables, raw olive oil...) was reduced to elimination the hepatic fat within 30-60 days[39-43]. Irisin, a hormone very recently discovered at Harvard Medical School, produced at mouse and human muscles may form the bases for new treatments against obesity and diabetes[44,45].

Recently it has been shown an association of visceral obesity and liver fat[46]. The metabolic active products of adipose tissue concern lipokines (TNF-

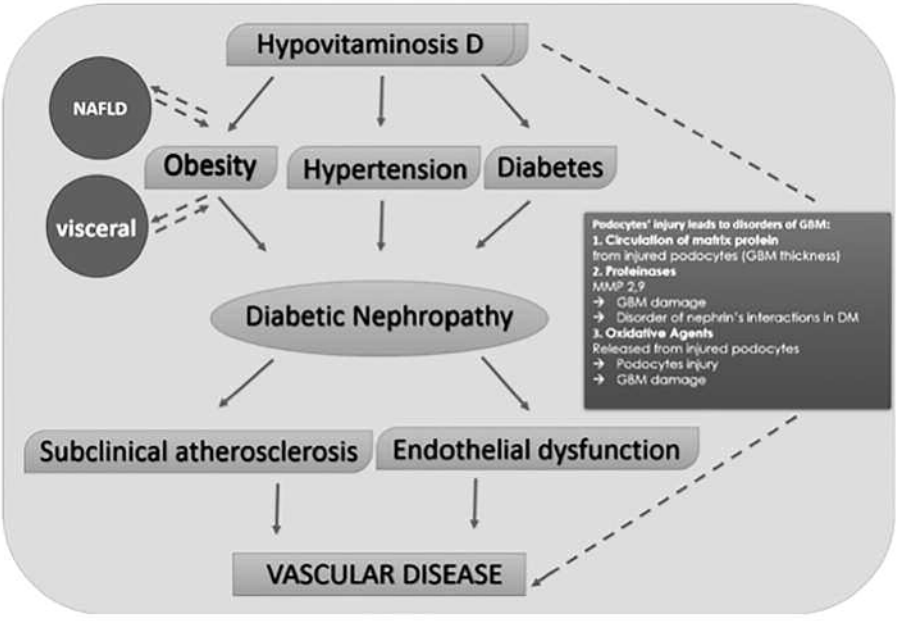

Figure 1. *Association of obesity, hypertension, diabetic nephropathy and vascular disease with hypovitaminosis D.*

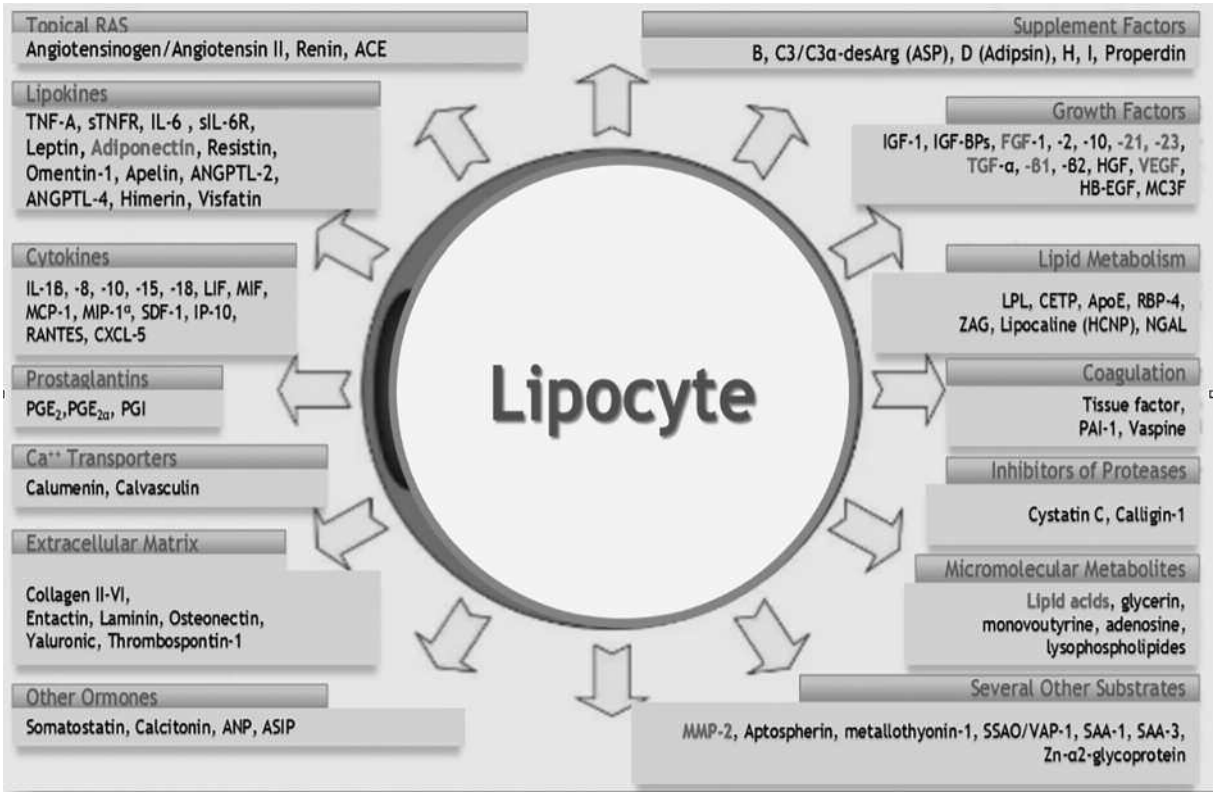

Figure 2. *Metabolic active products of adipose tissue.*

a, leptin, adiponectin), cytokines (MMP-2, IL-1β, IL-6), prostaglantins, extracellular matrix molecules (Col II-VI, laminin, yaluronic, thrombospontin), growth factors (IGF-1, FGF-1-2-10-21-23, TGF-a, VEGF), molecules of lipid metabolism (apo-E, NGAL), inhibitors of proteases (Cystatin C) and other substrates [fig. 2].

Fetuin A is a hepatokine that represents a key player in obesity, liver fat, diabetes, nephropathy and CVD. Fetuin A induces cytokine expression and suppresses adiponectin production[47]. It has been shown the association of fetuin A with insulin resistance and fat accumulation in the liver of humans[48]. Fetuin A is associated with diabetes type-2 and CVD[49,50].

Increased ECM production in fibrosis is due to overproduction of its physiological components, such as fibronectin, laminin, proteoglycans and type IV collagen, as well as the accumulation of proteins that do not normally occur in ECM, such as type I and III collagen in its mesangium glomerulus.

VEGF plays a major role to those interactions [fig. 3, 4].

Thus, the proposed human model includes diabetics with increased levels and vessels' expression of VEGF-A, FGF-23, fetuin-A, decreased levels of adiponectin and irisin, increased levels of IL-6 are associated in patients who will develop albuminuria and hypertension: from 4 to 10 fold higher.

VEGF-A g FGF-23 g Fetuin-Ag / Adiponecting / Irising IL-6

The disorders of filtration barrier in proteinuric disease include fusion of podocytes foot processes, detachment of podocytes loss in urine, focal and segmental stripping of GBM sections, focal adhesions of GBM with epithelial wall of Bowman's capsule leading to segmental glomerulosclerosis and loss of podocytes' number and finally proteinuria[51,52].

The causes of previous disorders concern detachment or apoptosis, absence of proliferation, DNA damage and hypertrophy[53].

Intact Podocytes are found in urine of glomerular disease, diabetic or not. More sensitive marker of renal damage than proteinuria is related to the intensity of proteinuria and the extend of glomerulosclerosis (detected when the number of podocytes is

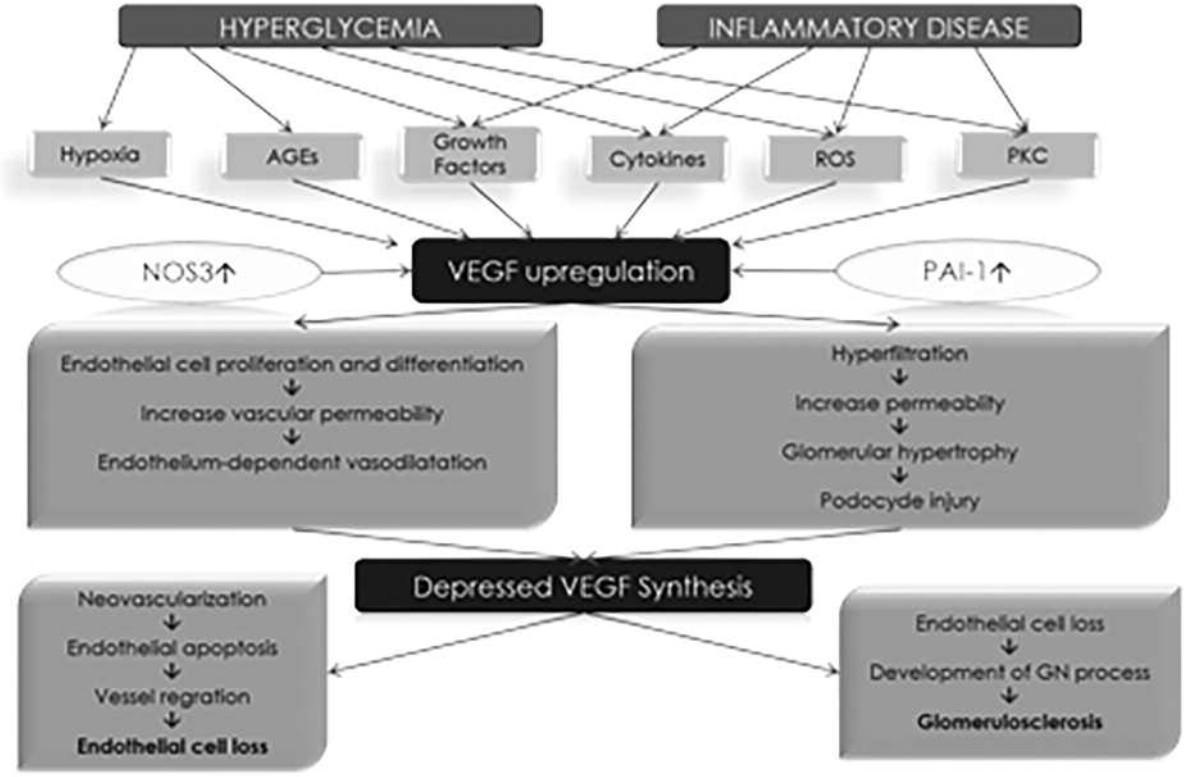

Figure 3. *Schematic overview of the role of VEGF in vessels and kidney alterations of Diabetic Nephropathy and Primary Chronic Glomerulonephritis.*

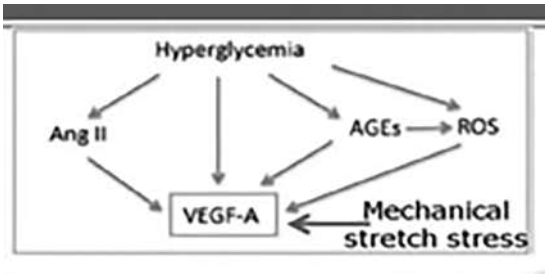

Figure 4. *Interactions of VEGF in Diabetes.*

reduced by 20%)[51-53]. Diabetic glomerular disease depends on podocyte number and this decrease seems more pronounced on the presence of NAFLD.

Disruption to any part of the filtration barrier may lead to proteinuria with or without fusion of podocyte foodpads. All three sections of the filtration barrier are in constant communication (molecular and biochemical) by interaction of extracellular matrix cells, growth factors (VEGF, TGF-β) and interaction of receptors – connectors[51-53].

Serra et al. studied the architecture of renal biopsies in 95 patients undergoing surgical treatment for severe obesity and had normal renal function. FSGS (Focal Segmental Glomerulosclerosis) was found in only 5/95 patients and not at all in the controls[54]. Increased mesangial hyperplasia, podocyte hypertrophy and generally glomerulomegaly were found more often in obese patients than in controls. This study showed that obesity increases the risk for both renal disease and chronic renal failure. Performing renal biopsy in relation with the study of renal function in patients with severe obesity without yet having impaired renal dysfunction (e.g. proteinuria) has helped enough the Nephrologists to investigate the pathophysiology of the kidneys and the pathogenesis of their histological damage[54].

In another recent study of Chen et al. concerning the investigation of obesity-related glomerulonephritis (ORG) of 90 patients it was found that most patients with ORG had normal renal function and FSGS[55].

However, a few studies have found NAFLD a risk factor associated with all-cause mortality, but these have been population-based studies with no mention of renal stages.

Although liver biopsy is the gold standard for the diagnosis of fatty liver disease, its invasive na-

ture clearly precludes its use in routine screening[56]. Fibroscan and magnetic resonance spectroscopy are more accurate techniques, but their use in the clinical setting is limited by their costs and availability[57]. Although ultrasound lacks sensitivity for the diagnosis of early steatosis in advanced CKD patients, due to increased renal cortical echogenicity in CKD, overall, because of its low cost, safety and accessibility, ultrasound is the recommended imaging technique for screening for fatty liver in the clinical and general population settings[56,57].

CKD patients are likely to be receiving RAS blockers, statins and some diabetics, metformin, which are all treatments used in management in NAFLD in the general population. Several scoring systems have been developed to help in early diagnosis, and utilization of other biomarkers may have a role in the future[56,57]. Further evaluation of the importance of NAFLD in the outcome of patients with advanced CKD should include consideration of concomitant treatments that might confound the results of studies.

ln conclusion, it is obvious that NAFLD is a strong and independent risk factor for cardiovascular events in patients with advanced CKD, a group already at high cardiovascular risk. The presence of NAFLD did not have an impact either on all-cause mortality or CKD progression. However, prospective studies with diagnostic techniques better suited to advanced CKD are needed to further evaluate the replicability of the findings described. We recommend the use of routine ultrasound screening for all higher risk CKD patients for early identification of this hidden risk factor so that targeted interventions can be planned to prevent future cardiovascular events.

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Diabetic cardiovascular autonomic neuropathy

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Diabetic Cardiovascular Autonomic Neuropathy (DCAN), the most studied form of Diabetic Autonomic Neuropathy, is a frequent and early complication of Diabetes, with a prevalence of around 20% in unselected patients[1].

The DCAN Subcommittee of Toronto Consensus Panel on Diabetic Neuropathy defines DCAN as an "impairment of cardiovascular autonomic control in patients with established diabetes after excluding other causes"[2].

Clinical correlates of DCAN are age, diabetes duration, glycaemic control, diabetic sensorimotor polyneuropathy and the microangiopathic diabetic complications; emerging ones are cardiovascular risk factors –such as blood pressure (BP)– and cardiovascular diseases[3]. Despite its prevalence, clinical and prognostic impact, DCAN is widely under-diagnosed[1].

The gold standard of diagnostic assessment of DCAN is cardiac autonomic reflex tests (CARTs). They are based on heart rate, blood pressure, and sudomotor responses and were discovered by Ewing et al. in the 1970s[5]. CARTs involve measuring autonomic responses through changes in heart rate (HR) variability and blood pressure (BP). Sympathetic function is assessed by BP response to postural changes, the Valsalva maneuver. Parasympathetic function is assessed by HR response to deep breathing, changes in posture (i.e., lying to standing), and the Valsalva maneuver[6,7]. In the autonomic reflex tests, the HR response to respiration is measured as the expiration to inspiration (E:I) ratio, which measures beat to beat sinus arrhythmia (R-R variation) during paced deep expiration and inspiration. Heart rate is measured via electrocardiogram with the patient in the supine position and breathing at 6 breaths per minute (bpm); a difference of >15 bpm is considered normal. Heart rate response to standing is known as the 30:15 ratio and usually consists of an initial increase and then decrease in HR[7,8]. In this test, the R-R interval is measured at 15 beats and 30 beats after standing, with the normal value > 1.03[6,7,9]. Heart rate response to Valsalva involves an initial increase in HR followed by an excessive decrease in HR, and the normal ratio of longest to shortest R-R interval is >1.2[7,8,10]. Sympathetic function is assessed by noting changes in systolic BP in the supine position and again after standing for 2 minutes, with normal being a fall of < 10 mm Hg[7,10].

The Toronto Consensus recommends that diagnosis of DCAN be based on the use of CARTs, i.e., heart rate response to deep breathing, standing, Valsalva maneuver, and BP response to standing, and that more than one heart rate test and OH test are required. Moreover, the performance of CARTs should be standardized, the influence of confounding variables minimized, and age-related normal ranges of heart rate tests strictly required[11].

The DCAN Subcommittee of Toronto Consensus Panel on Diabetic Neuropathy recommends that patients with Type 2 Diabetes Mellitus (T2DM) be screened for DCAN at the time of diagnosis and those with Type 1 Diabetes Mellitus (T1DM) within 5 years of their diagnosis, especially in patients exhibiting multiple risk factors, such as poor glycemic control, smoking, hypertension, or dyslipidemia. The Panel also recommends that screening be part of a perioperative risk assessment in patients with coronary artery disease[5]. Similarly, guidelines from the American Diabetes Association (ADA) recommend that diabetic patients displaying common DCAN symptoms—such as lightheadedness, weakness, palpitations, and syncope that occurs on standing—undergo further assessment to rule out causes other than CAN, especially if they have microvascular and/or neuropathic complications or hypoglycemia unawareness[5,6].

The role of intensive diabetes therapy in delaying the development of DCAN in T1DM is confirmed, whereas only limited evidence exists for intensive multifactorial intervention in T2DM. On the other hand, symptomatic treatment of clinical correlates of DCAN like Orthostatic Hypotension is available and advisable[11].

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Diabetic peripheral vascular disease

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Peripheral artery disease (PAD) is a common manifestation of atherosclerotic cardiovascular disease, estimated to affect approximately more than 200 million people worldwide[1]. Regardless of the improvements of diagnostic tools and techniques, PAD is still a difficult disease for diagnosis, due to the fact that only 10% of patients present with classic symptomatology and up to two-thirds of them are asymptomatic. In case of late diagnosis, high degree of ischemia leads to critical ischemia and ulcer which in turn leads to gangrene. Diabetes, which is one of the major/ most common risk factors for PAD, leads to increased glucose levels that cause microvascular and macrovascular complications such as peripheral neuropathy and angiopathy[2]. This situation causes tissue damage and diabetic foot. Characteristics of diabetic foot are infection, ulceration and destruction of deep tissue associated with neurological abnormalities and various degrees of peripheral vascular disease on the lower limb. When the damage is irreversible, the only solution is amputation. It has been confirmed that 25% of patients with diabetes will face ulcers during their lifetime and one quarter of people with ulcers on lower limb needs continuous hospitalization. These patients present arterial lesions below the knee and below the ankle and their most common problem is multilevel stenosis/occlusion of femoral, popliteal, peroneal and tibial vessels[3]. Ulcers on lower limb require an expert medical team of different specialties including endocrinologist, dermatologist, orthopedic, plastic and vascular surgeon[4]. This team evaluates the ulcer, looking for necrosis or gangrene, signs of infection such as fever, redness, swelling or even metabolic instability. They also examine if the ulcer has foul-smelling discharge, possible secretion or pain. A large percentage of diabetic ulcers become infected and 20% of patients with infected lower limb injury will undergo amputation.

In order to examine blood circulation, it is essential to identify peripheral pulses in the arteries of the lower limb. If the hospital or the medical center provides Doppler device, the medical staff measures the ankle – brachial Index (ABI) which is an indicator of blood circulation of the lower limb[5].

Open surgical arterial bypass and endovascular procedure are the most common techniques of treatment in patients with foot ulcers.

Open surgical arterial bypass is characterized by several disadvantages. These include general anesthesia, surgical trauma, arterial clamping and declamping, blood loss, infections, prolonged hospitalization and systematic complications. On the contrary, endovascular procedure reduces the complications of surgery, improves wound healing and minimizes amputation rates as well as the risks of anesthesia since it is local. However, there are not sufficient data to demonstrate whether endovascular or open revascularization provides an advantageous approach in treatment of symptomatic peripheral arterial disease. Current literature argues that endovascular procedure has recently –in terms of quantity– become the preferred method[6].

Finally, it is essential to decide the immediate revascularization of lower limb when it is appropriate. The decision on whether, and when, to revascularize in a patient with diabetic foot ulceration and peripheral arterial diseases is complicated[7]. It is recommended an initial trial of non-operative management for patient swith mild PAD (ABPI≥0.6, TcPO2>50 mmHg, toe pressure>55 mmHg), comprising optimization of risk factors (control of blood pressure, hyperlipidemia, plaque stabilization with statins, smoking cessation, glycemic control) offloading, debridement and treatment of infection.Response should be monitored closely and revascularization considered after 4-6 weeks, if there is no evidence of woundhealing[8]. Further guidelines recommend that revascularization (either endovascular or surgical bypass) should be considered in a person with diabetic foot ulceration with evidence of peripheral arterial disease of sufficient severity to hamper wound healing, unless that patientis deemed unsuitable for intervention because of functional or medical comorbidities, or when the foot is considered functionally unsalvageable[9]. It is also acceptable that revascularization is appropriate if healing does not occur despite optimum conservative management[10]. Therefore, the combination of clinical examination and careful interpretation of perfusion along with consideration of the wound and infection extent is required to select patients appropriately for revascularization[11].

In conclusion, early endovascular revascularization and local surgical treatment contributes in limiting amputation levels[12].

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Cardiovascular safety of new drugs for the treatment of obesity and diabetes

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In the past, several anti-diabetic agents under development or already approved, including Muraglitazar, a dual peroxisome proliferator-activated receptor (PPAR) agonist and Rosiglitazone (a Thiazilidinedione) gave rise to valid concerns about adverse cardiovascular events, further enhanced by the results of the ACCORD Study in 2008.

In response to the above in July 2008, the FDA's Endocrinology and Metabolism Advisory Committee issued new industry guidelines on the assessment of cardiovascular risk of anti-diabetic agents before and after market placement. These guidelines have led to radical changes in the evaluation process for all new anti-diabetic drugs being evaluated and /or already on the market. These guidelines have led to double of the number of clinical trials of cardiovascular outcomes and a six-fold increase in the median number of patients participating in cardiovascular trials, in the first 36 months.

Epidemiological evidence suggests a close relationship between plasma glucose levels, morbidity and mortality in Type 2 Diabetes (T2D). Although many trials have shown significant benefits to micro-vascular outcomes from lowering glucose levels, no consistent data on the effects on macro-vascular events were evident.

A meta-analysis of the UKPDS, PROactive, ADVANCE, VADT and ACCORD studies demonstrated cardiovascular benefits from intensive glucose-lowering therapy. After approximately 5 years of treatment, a 0.9% decrease in HbA1c resulted in a significant reduction in non-fatal myocardial infarction and coronary heart disease and a non-significant reduction in stroke. There was no benefit in mortality reduction from all causes. Indeed, the ACCORD trial was discontinued early after 3.5 years, due to high mortality rates among participants with a HbA1c <6.0% primary target.

Therefore there is still a need for a safe and effective antidiabetic treatment that offers both glycemic control and macro-vascular benefits in T2D patients. This is a more moderate effect than the number of events prevented for each of 4 mmHg drop in blood pressure or for any decrease in LDL cholesterol. This demonstrates the importance of a multi-intervention approach in the treatment of T2D patients to reduce cardiovascular risk.

With regards to Metformin and CV outcomes related to its prescription, the UKPDS study (1998) provides evidence for the beneficial CV effects of metformin. In the UKPDS 34 study, the metformin group had a 39% lower risk of myocardial infarction (MI) than the conventional treatment group ($p = 0.01$). The significant reduction in MI risk endured for over 10 years. Metformin added to Sulphonylurea (SU) vs SU alone, was associated with increased risk of diabetes-related death (RR of 1.96, $p = 0.039$) and all-cause mortality (RR of 1.60 $p = 0.041$). In the UKPDS 34 study, overweight patients treated with metformin had reduced risk for any diabetes-related endpoint, diabetes-related death and all-cause mortality.

The PROactive study demonstrated that pioglitazone was not significantly superior to placebo for the primary endpoint, which was the composite of all-cause mortality, non-fatal MI (including silent MI), stroke, acute coronary syndrome (ACS), endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. However, pioglitazone was significantly superior to placebo for the secondary endpoint key, which was the composite of all-cause mortality, non-fatal MI and stroke.

Studies on ddp4 inhibitors (TECOS, EXAMINE, SAVOR-TIMI, CAROLINA, CARMELINA) demonstrated cardiovascular safety but not superiority, and in the case of saxagliptin (SAVOR-TIMI) increased risk of hospitalization for heart failure.

The most significant results were seen in the Sodium-glucose co-transporter-2 (SGLT2) inhibitors category, where studies (EMPAREG, CAMVAS, DECLARE-TIMI) showed not only safety but in many drugs, significant benefits for cardiovascular, renal symptoms and heart failure symptom management opening new paths of scientific enquiry.

Glucagon-like peptide 1 (GLP-1) receptor agonists Liraglutide, Semaglutide and Dulaglutide (LEADER, SUSTAIN, REWIND) studies showed significant benefits in reducing CV and renal events while other studies for drugs in same category demonstrated their safety (ELIXA, EXCEL). Newer insulins have also proven safe for any GLP-1 molecules that have been studied (DEVOTE).

In direct contrast to the CV related anti-diabetic studies, obesity related research has not shown the same progress. Many anti-obesity agents were withdrawn and those that are still available come with important safety warnings. With the possible exception of Liraglutide (approved for medical use in Europe in 2009 and in the United States in 2010) there is not much to say about cardiovascular safety for this category of agents.

In conclusion, for T2D, following the guidelines for cardiovascular safety studies, anti-diabetic agents are safe and in many cases with significant benefits for other comorbidities, while for obesity we cannot say the same as the agents currently on market do not inspire that level of safety.

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Diabetic Autonomic Neuropathy and Cardiovascular Function

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Diabetic neuropathy has been defined as a set of clinical and subclinical syndromes that affect distinct regions of the nervous system, with differing clinical courses, singly or combined and possibly differing underlying aetiopathogenetic mechanisms. Each is characterized by generalized or focal damage to peripheral somatic or autonomic nerve fibers resulting from diabetes mellitus. The syndromes may be grouped under two general headings: generalized and focal neuropathies. The generalized neuropathies, i.e., distal symmetrical sensorimotor polyneuropathy (DPN) and diabetic autonomic neuropathy (DAN) are common, usually chronic, frequently coexist and often progressive. The focal neuropathies are less common, usually acute in onset, and often self-limited.

Generalized Diabetic Neuropathy is the most common, underdiagnosed and poorly treated microvascular complication of diabetes mellitus. Diabetic neuropathy is a major factor in the impaired wound healing, erectile dysfunction, and cardiovascular dysfunction. More than half of all individuals with diabetes eventually develop neuropathy with a lifetime risk of one or more lower extremity amputations estimated in some populations to be up to 15%. Disease progression in neuropathy was traditionally clinically characterized by the development of vascular abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia with subsequent diminishment in oxygen tension and hypoxia.

Hyperglycemia clearly plays a key role in the development and progression of diabetic neuropathy as well as the other microvascular complications of diabetes. Excess intracellular glucose is processed by increased flux through one or more glucose metabolism pathways, and prolonged hyperglycemia can lead to increased oxidative and nitrosative stress, defective neurotropism, and autoimmune-mediated nerve destruction which could result to cellular damage in several ways. Cells within tissues that are prone to diabetic complications, such as endothelial cells, are not able to modulate glucose transport rates to prevent excessive accumulation of glucose in intracellular space. Another consequence of excess intracellular and extracellular glucose is the generation of advanced glycation end products (AGEs), via attachment of reactive carbohydrate groups to proteins, lipids, or nucleic acids. The main mechanisms behind the tissue damage caused by AGEs are intracellular

glycation, cross-link formation, and interaction with RAGEs. These groups tend to impair the biological function of proteins, thus affecting cellular function.

Cardiovascular Autonomic Neuropathy (CAN) has been linked to resting tachycardia, postural hypotension, exercise intolerance, reduced heart rate variability, enhanced intraoperative or perioperative cardiovascular liability, increased incidence of asymptomatic ischemia, silent MI, and decreased rate of survival after myocardial infarction. Resting tachycardia and a fixed heart rate are characteristic late findings in diabetic patients with vagal impairment, whereas abnormalities in heart-rate variability (HRV) are early findings of CAN. The prognostic value of resting heart rate is a useful tool for cardiovascular risk stratification and as a therapeutic target in high-risk patients.

In particular exercise intolerance due to CAN is a major problem, because of lifestyle guidelines, which recommend programs of exercise. Diabetic patients who are likely to have CAN should be tested for cardiac stress before undertaking an exercise program. Patients with CAN need to rely on their perceived exertion, not heart rate, because a "locked" heart rate and Left Ventricular dysfunction could co-exist, in order to avoid hazardous levels of intensity of exercise. Moreover in our studies we showed that CAN associated significantly with Left Ventricular Dysfunction. Cardiovascular diabetic autonomic neuropathy is a complication related to poorly controlled diabetes and includes abnormalities in heart rate control, vascular hemodynamics, and cardiac structure and function. Perioperative cardiovascular morbidity and mortality are increased 2- to 3-fold in patients with diabetes and preoperative cardiovascular autonomic screening of diabetic patient may help anesthesiologists identify those at greater risk of intraoperative complications.

Orthostatic hypotension is defined as a decrease in blood pressure (ie, >20 mmHg for systolic or >10 mmHg for diastolic) in response to postural change, from supine to standing. In patients with diabetes, orthostatic hypotension is usually a result of damage to the efferent sympathetic vasomotor fibers, particularly in the splanchnic vasculature.

Patients may present with light-headedness and presyncopal symptoms, or may remain asymptomatic despite significant drops in blood pressure. Orthostatic symptoms can also be misjudged as hypoglycemia and can be aggravated by several drugs, including vasodilators, diuretics, phenothiazines, and particularly TCAs and insulin.

Symptoms usually occur with advanced disease, and screening of diabetic patients for CAN is essential. The Cardiovascular Autonomic Reflex Tests (CARTs) are the gold standard. Restoration of autonomic balance is possible and has been shown with strict glycolic control, therapeutic lifestyle changes, increased physical activity, and diabetes treatment (ACE inhibitors, b-adrenergic blockers and potent antioxidants, such as a-lipoic acid).

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

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

- 11-15 November 2020, **Thessaloniki**
  34th Panhellenic Annual Conference
  Hotel "Makedonia Palace"
- 15 November 2020, **Thessaloniki**
  Meeting for the public
  Hotel "Makedonia Palace"

For more information: www.hasd.gr