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Influence of Storage and Inter- and Intra-Assay Variability on the Measurement of Inflammatory Biomarkers in Population-Based Biobanking

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Background: In the present study, we examined the effect of sample storage on the reproducibility of several inflammatory biomarkers, including high-sensitivity C-reactive protein (hsCRP), high-sensitivity interleukin-6 (hsIL6), and high-sensitivity tumor necrosis factor alpha (hsTNFα). In addition, we assessed inter- and intra-assay variability between collaborating biobanks.
Methods: In total, 240 fasting plasma samples were obtained from the LifeLines biobank. Samples had been stored for less than 2 or more than 4 years at −80°C. Measurements were performed at three different laboratories. hsCRP was measured by immunonephelometry and ELISA, hsIL6, and hsTNFα samples were measured with ELISAs from two different manufacturers. For confirmation, similar analyses were performed on samples obtained from a subpopulation of 80 obese individuals. Passing–Bablok regression analysis and Bland–Altman plots were used to compare the results.
Results: We observed good stability of samples stored at −80°C. hsCRP measured on the day of blood draw was similar to levels measured after more than 4 years of storage. There were small interlaboratory differences with the R&D ELISAs for hsIL6 and hsTNFα. We found a linear correlation between the Bender Medsystems ELISA and the R&D ELISA for hsIL6, with significantly higher levels measured with the R&D ELISA. Over 90% of hsTNFα samples measured with the IBL ELISA were below the detection limit of 0.13 ng/L, rendering this assay unsuitable for large-scale analysis. Similar results were found in the confirmation study.
Conclusion: In summary, plasma hsCRP showed good stability in samples stored for either less than 2 years or more than 4 years at −80°C. Both the R&D and Bender Medsystems for hsIL6 measurement yielded similar results. The IBL hsTNFα assay is not suited for use in biobanking samples. Assays for the measurement of inflammatory biomarker assays should be rigorously tested before large sample sets are measured.

Keywords: biobanking, assay, storage, variability, ELISA, nephelometry

Introduction

Population-based biobanks are involved in processing and storage of biospecimens for future studies and have, sometimes over decades, also accumulated epidemiological data. Several new biobanking initiatives have been launched, building on these strengths. The Biobank Standardization and Harmonisation for Research Excellence in the European Union (BioSHaRE-EU) project is based on international collaborative projects between European and

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Canadian institutes and European cohort studies. The project has developed and applied several methods and tools for harmonization and standardization in European biobanks and major biomedical studies.[1] If an efficient organization of these existing resources is implemented, rapid progress can be achieved. This has been impressively demonstrated by the success of genome-wide association studies (GWAS) and the combined analysis of these data in large meta-analyses.[2]

For other new research fields such as metabolomics[3] and epigenomics,[4] the availability of samples of high quality is important. Standardization of sample collection, preanalytics, and harmonization and standardization of high-throughput assays to measure biomarkers such as inflammatory biomarkers are crucial.[5,6] In general, biomarkers are defined as objectively measurable indicators for biological or pathobiological processes or pharmacological responses toward medical treatment.[7] Biomarkers may serve as surrogate endpoints that correlate with clinical endpoints, indicate disease progression and regression under therapy, and may allow outcome prediction. For optimal collaboration between cohort studies or biobanks, harmonization and standardization of analytical procedures of biomarker measurements are essential. Analytical results may be affected by preanalytical conditions and analytical variability.[6,8] For example, different types of samples may be available for analyses, but may yield different results upon measurement (e.g., serum vs. plasma).

Furthermore, biobanks often use samples that may have been stored at different temperatures or storage duration,[9–11] and the amount of sample material may be very limited. Therefore, evaluating the stability of stored samples is important. Finally, results may be based on the use of different assays, techniques, or equipment.

Studies investigating the variability of sample processing, different assays, use of different sample types, and reproducibility of archived samples are scarce, particularly with regard to measurement of inflammatory biomarkers such as cytokines.[12] Aziz et al. examined preanalytical variables on high-sensitivity C-reactive protein (hsCRP) and found that hsCRP levels in serum were not significantly different from plasma samples.[13] In addition, storage of samples at −70°C for 3 weeks had no effect on hsCRP concentrations. However, some contradictory data regarding long-term storage of hsCRP exist.[14,15] Only a few studies have evaluated and compared different assays to measure other inflammatory markers. Lopez-Campos et al. compared enzyme-linked immunosorbent assay (ELISA) with immunonephelometry for the measurement of hsCRP in patients with stable COPD.[16] Although the serum hsCRP concentrations measured by ELISA and nephelometry correlated well, concentrations measured using ELISA tended to be lower.

The present study aimed to assess the reproducibility of several inflammatory biomarkers after storage for either less than 2 years or more than 4 years at −80°C. In addition, we examined inter- and intra-assay variability for the measurement of hsCRP, high-sensitivity interleukin-6 (hsIL6), and high-sensitivity tumor necrosis factor alpha (hsTNFα) between collaborating biobanks. The IBL hsTNFa assay and Bender MedSystems hsIL6 assay were specifically chosen for comparison because they use a smaller sample volume than the R&D ELISA.

Materials and Methods

Participants and sample collections

Subjects included were participants from the LifeLines Cohort Study.[17] Lifelines is a multidisciplinary, prospective, population-based cohort study examining, in a unique three-generation design, the health and health-related behaviors of persons living in the north of The Netherlands. It started in 2007 and employs a broad range of investigative procedures in assessing the biomedical, sociodemographic, behavioral, physical, and psychological factors that contribute to the health and disease of the general population, with a special focus on multimorbidity and complex genetics. The methodology has been described previously.[18] All participants were between 18 and 90 years old at the time of enrollment. They provided written informed consent before participating in the study. The study protocol was approved by the medical ethics review committee of the University Medical Center Groningen (UMCG).

Laboratory measurements

For the current study, a 900-μL plasma sample from each of the 240 participants was selected by the LifeLines Scientific Bureau according to the study proposal. Blood samples were obtained from healthy individuals ($n=80$), individuals with type 2 diabetes ($n=80$), and those with clinical macrovascular disease who reported a previous myocardial infarction ($n=80$). All samples had been drawn by venipuncture in the fasting state, between 8 and 10 a.m. After blood withdrawal, the EDTA tubes were transported at 4°C (1.5 hours) to the LifeLines laboratory. Tubes were centrifuged directly after arrival, and plasma was stored in 0.9-mL aliquots in Thermo Scientific Matrix 2D barcoded 1.0-mL tubes at −80°C. Only hsCRP was measured on the same day at the department of clinical chemistry at UMCG.

For the current study, stored samples were thawed once and aliquoted in a 96-well polystyrene microplate and stored again at −80°C before shipment on dry ice 1–2 weeks later to the laboratories in Trondheim, Norway, Ulm in Germany, and the department of clinical chemistry at UMCG, where analysis was performed within 2–4 weeks after receipt. The laboratories have been indicated in this article with a letter (allocated by random number).

More information on the distribution of the samples over the three locations and detection limits of specific assays, as well as storage time, is given in Figure 1 and Table 1.

Serum hsCRP was measured at the day of blood collection at the LifeLines laboratory using latex-enhanced immunonephelometry (Siemens Healthcare Diagnostics). Standardization was based on protein reference ERM DA 470 (CRM 470). The results of the baseline hsCRP measurements were compared with the results from 4-year stored samples using immunonephelometry. Interassay comparison was examined for the R&D ELISA (location A) and immunonephelometry (location C). Due to the limited amount of sample, we skipped hsCRP measurements at location B beforehand.

The R&D ELISA for hsIL6 measurement was used both at locations A and C and used 100 μL of the sample for analysis. The Bender MedSystems ELISA kit (location B) was specifically chosen as it used a smaller volume of sample (50 μL) for analysis. Measurement of hsIL6 with the Bender MedSystems ELISA was compared with the R&D ELISA at location C.

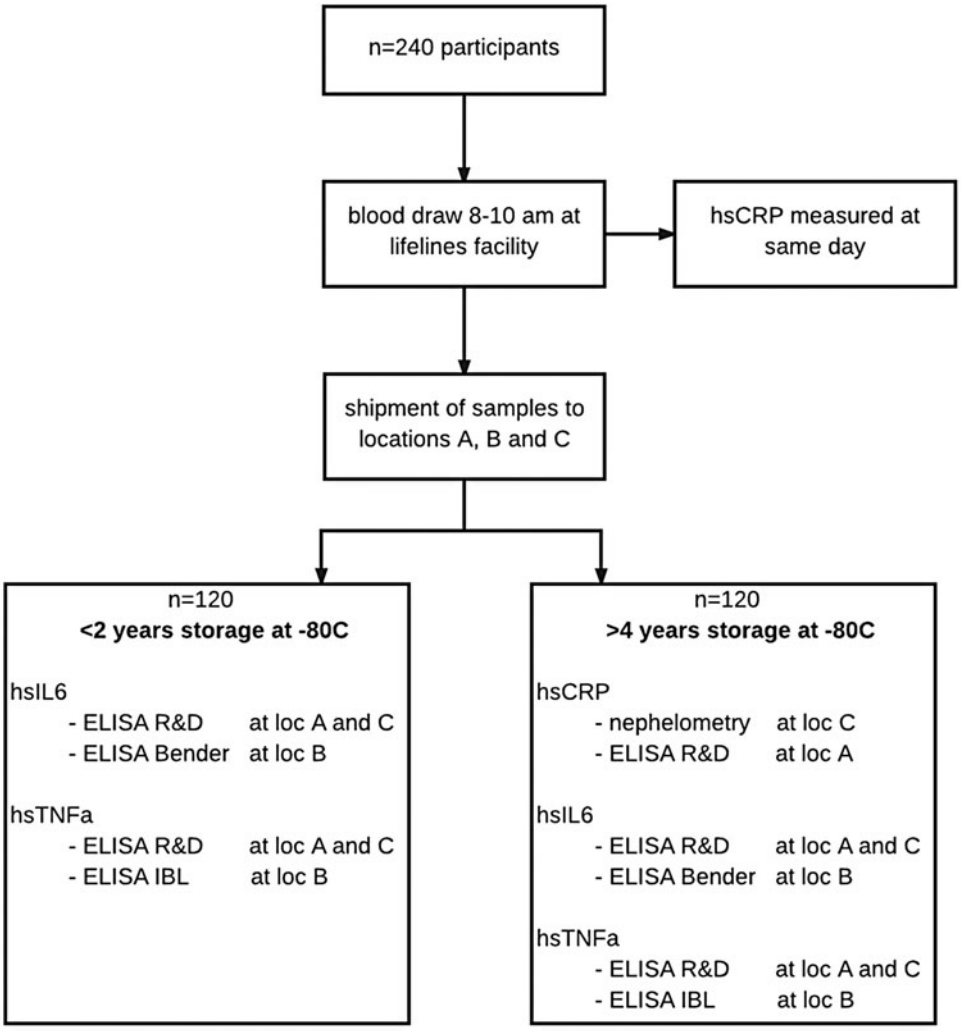

FIG. 1. Flowchart showing the distribution of samples for the three locations. Location B: hsCRP measurement was not performed due to limited amount of sample (0.9 mL) available for the total set of experiments. All samples underwent one freeze–thaw cycle. hsCRP, high-sensitivity C-reactive protein.

The IBL ELISA (location B) for the measurement of hsTNFα was specifically chosen for comparison, as it uses a smaller volume of sample (50 μL), and was compared with the R&D ELISA used at location C.

For validation of initial results, additional analyses of plasma hsIL6 and hsTNFα were performed by one dedicated analyst in a set of 80 samples obtained from obese individuals who participated in a weight reduction program in The Netherlands (the LOWER study, www.clinicaltrials.gov, NCT00862953). Those samples had been stored at −80°C for an average period of 5.5 (range 4–7) years. The results of hsIL6 measurement using the R&D ELISA were compared with the results obtained by the Bender MedSystems. The results of hsTNFα measurement using the IBL ELISA were compared with the results obtained by the R&D ELISA.

Statistical analyses

Statistical analyses were performed using SPSS, version 22. Passing–Bablok regression analysis and Bland–Altman plots were created with MedCalc (MedCalc, Ostend, Belgium) to evaluate inter- and intra-assay variation, also between

Table 1. Assay Overview for Different Inflammatory Biomarkers

Inflammatory biomarker	*Assay*	*Producer*	*Standardization*	*Detection limit*	*Lowest vs. highest standard*	*Intra-assay variation*	*Interassay variation*
hsCRP	ELISA	R&D systems	NIBSC 85/506	0.010 mg/L	0.78–50 mg/L	4.4%	6.0%
hsIL6	ELISA	R&D systems	NIBSC 89/548	0.039 ng/L	0.156–10 ng/L	6.9%	9.6%
hsTNFα	ELISA	R&D systems	NIBSC 88/786	0.106 ng/L	0.5–32.0 ng/L	8.7%	10.4%
hsIL6	ELISA	Bender MedSystems	NIBSC 89/548	0.030 ng/L	0.08–5.0 ng/L	4.9%	6.0%
hsTNFα	ELISA	IBL International	NIBSC 87/650	0.130 ng/L	0.31–20.00 ng/L	8.5%	9.8%
hsCRP	Nephelometry	Siemens Healthcare	CRM 470	0.175 mg/L	0.175–11.00 mg/L	7.6%	unknown

Table 2. Baseline Characteristics of the 240 Participants in the LifeLines Cohort Study

	Healthy	*Post-MI*	*Type 2 diabetic*
	N = 82	N = 83	N = 75
Male/female	44/38	61/22	32/43
Age (yrs)	54 ± 11	63 ± 10	62 ± 11
BMI (kg/m2)	25.7 ± 3.0	28.0 ± 3.8	30.1 ± 4.5
Fasting blood glucose (mM)	4.9 ± 0.5	5.5 ± 0.9	7.6 ± 1.9
HbA1c (%)	5.6 ± 0.3	5.9 ± 0.5	7.0 ± 1.0
Total cholesterol (mM)	5.6 ± 1.0	4.6 ± 1.1	4.4 ± 0.9
HDL-cholesterol (mM)	1.52 ± 0.39	1.29 ± 0.36	1.28 ± 0.29
LDL-cholesterol (mM)	3.67 ± 0.91	2.86 ± 0.97	2.58 ± 0.80
Triglycerides (mM)	1.10 (0.86–1.54)	1.13 (0.91–1.64)	1.48 (1.14–1.91)

different laboratories, as well as the influence of storage (time) on the measurement of hsCRP, hsIL6, and hsTNFα.

Results

The characteristics of the study population are shown in Table 2. Individuals who had suffered from an MI were older than healthy subjects and those with type 2 diabetes. Both BMI and hsCRP levels were highest among subjects with type 2 diabetes compared with subjects from the other two groups.

Nephelometry was used to compare the hsCRP results from baseline measurement with the results from samples stored for more than 4 years. Both Figure 2 and Supplementary Figure S1 (Supplementary Data are available online at www.liebertpub.com/bio) show identical results for both the baseline samples and samples that had been stored for more than 4 years. For the interassay comparison between the R&D ELISA and immunonephelometry, 200 of the 240 plasma samples were available for analysis; 3 samples were below the detection limit of the ELISA, while 37 samples were above the detectable range.

These samples were not measured again in dilution due to insufficient sample material. Plasma hsCRP levels measured by the R&D ELISA tended to be lower than levels measured with immunonephelometry (Fig. 3 and Supplementary Fig. S2).

Regarding hsIL6, there were significant differences in the results, as well as differences regarding the detection limit. The R&D ELISA yielded similar results in both laboratories (locations A and C) except for some outliers (Fig. 4).

However, at location A, 38 samples were below the detection limit of the assay, whereas at location C, using the same ELISA, 2 samples had concentrations above 5 ng/l. Next, a linear correlation was found between the results obtained using the Bender MedSystems ELISA (location B) and the R&D ELISA (location C), but with statistically significant higher levels measured by the R&D assay (Fig. 5 and Supplementary Fig. S3). These results were comparable for samples stored up to 2 years and samples stored for more than 4 years showing no effect of storage time on sample stability. With the Bender MedSystems ELISA used at location B, two samples could not be measured due to insufficient sample material, while three samples were below the detection limit of the assay.

The R&D ELISA for hsTNFα was used at locations A and C. Unfortunately, 177 samples were lost for evaluation due to an error by a technician at location A. Despite

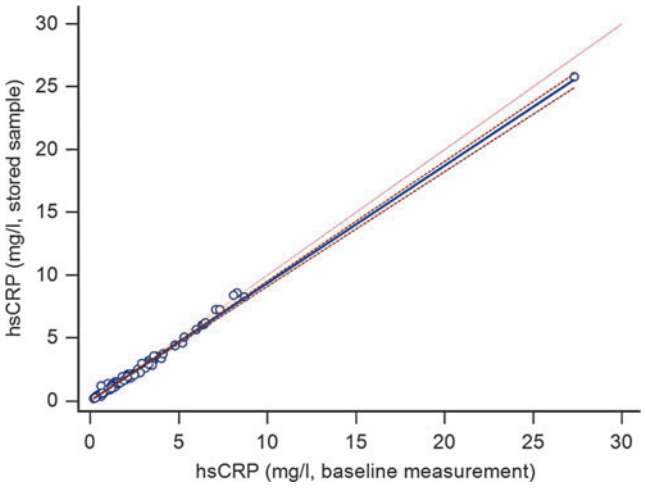

FIG. 2. Passing–Bablok correlation between plasma hsCRP measured at the day of blood collection and in plasma samples stored for more than 4 years. All the samples were measured using nephelometry. $N = 116$ samples measured at baseline (the day of blood collection) and after >4 years of storage, in 124 samples, no measurements of hsCRP were performed during screening of the participant.

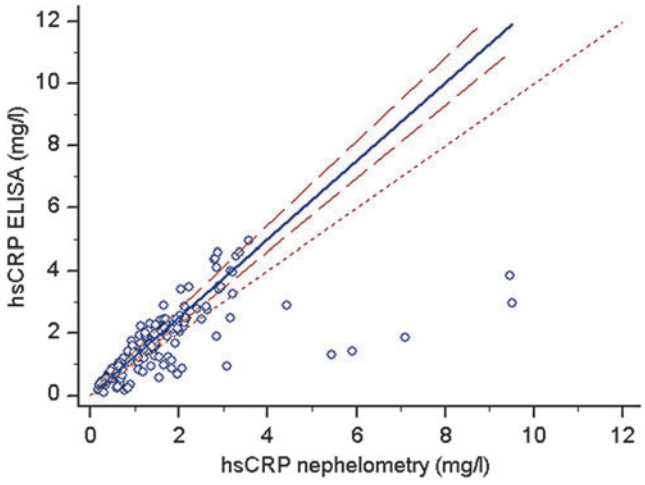

FIG. 3. Passing–Bablok correlation for stored plasma hsCRP samples measured with nephelometry (location C) and R&D ELISA (location A). Stored hsCRP samples measured at two locations using different assays. Location A used the R&D ELISA, whereas location C used nephelometry. Two hundred of the 240 samples were available for analysis; 3 samples were below the detection limit of the ELISA, while 37 samples were above the detectable range.

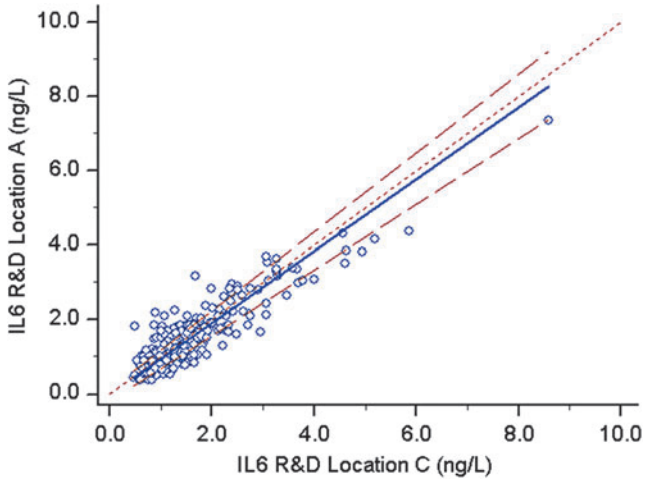

FIG. 4. Passing–Bablok correlation for plasma hsIL6 measured with R&D ELISA (location C vs. location A). Stored hsIL6 samples measured at two locations using the same ELISA. Both locations A and C used the R&D ELISA. Two hundred of the 240 samples were available for analysis. At location A, 38 samples were below the detection limit of the assay, whereas at location C, using the same ELISA, 2 samples had concentrations above 5 ng/L. hsIL6, high-sensitivity interleukin 6.

this, a reasonable agreement in the hsTNFα results between locations A and C was observed, except for some outliers (Fig. 6). Since there were only 4-year stored samples available, we were not able to examine the effect of storage time on the samples. At location B, using the IBL ELISA, only 16 samples yielded feasible and measurable results. All other samples proved to be below the detection limit of 0.13 ng/L (Fig. 7).

For confirmation and replication, we performed an additional evaluation of assays for the measurement of plasma hsTNFα

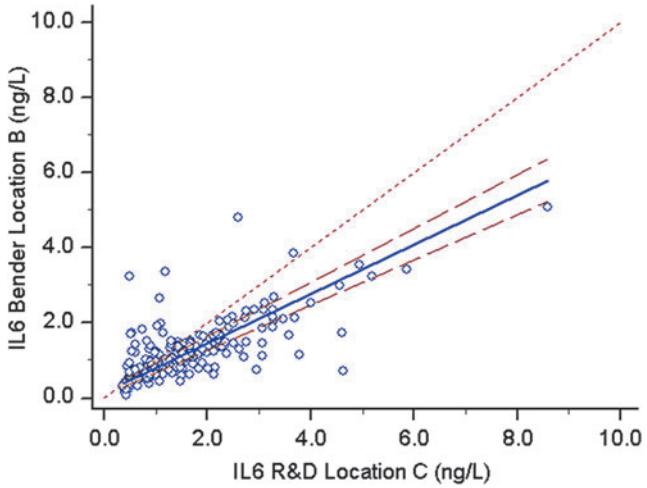

FIG. 5. Passing–Bablok correlation for plasma hsIL6 measured with R&D ELISA (location C) and Bender MedSystems (location B). Stored hsIL6 samples measured at two locations using different ELISAs. Location B used the Bender MedSystems ELISA, while Location C used the ELISA from R&D. Two hundred thirty-three of the 240 samples were available for analysis, 4 samples could not be measured due to insufficient sample material, while 3 samples were below the detection limit of the assay.

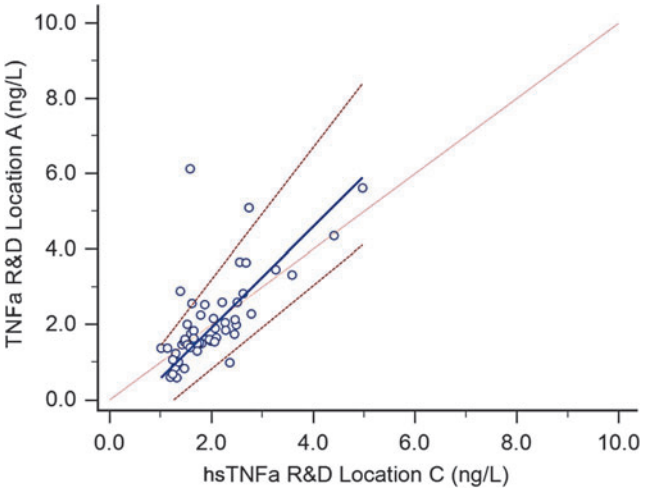

FIG. 6. Passing–Bablok correlation for plasma hsTNFa measured with R&D ELISA (location C vs. location A). Stored hsTNFa samples measured at two locations using the same ELISA. Both locations used the R&D ELISA. At location C, one serum sample yielded a result >16 ng/mL. At location A, 7 samples were below the detection limit and one sample yielded results above the detection limit. However, 177 samples (3 ELISA kits) were lost for evaluation due to an error. Only 54 samples could be compared with the results in location C. hsTNFa, high-sensitivity tumor necrosis factor alpha.

and hsIL6 in stored samples (mean 5.5 years, range 4–7 years) obtained from a population of 80 obese individuals (50% males, mean age 52 ± 12 years, BMI 38.0 ± 6.2 kg/m^2) participating in a weight reduction program. For hsIL6, an excellent correlation was found regarding the results obtained by the R&D ELISA and the Bender MedSystems ELISA (Fig. 8). However, regarding hsTNFα measurements, poor results for the IBL ELISA compared with R&D ELISA, already described above, were confirmed: 66 of 80 samples yielded results below the detection limit set by the manufacturer (Fig. 9).

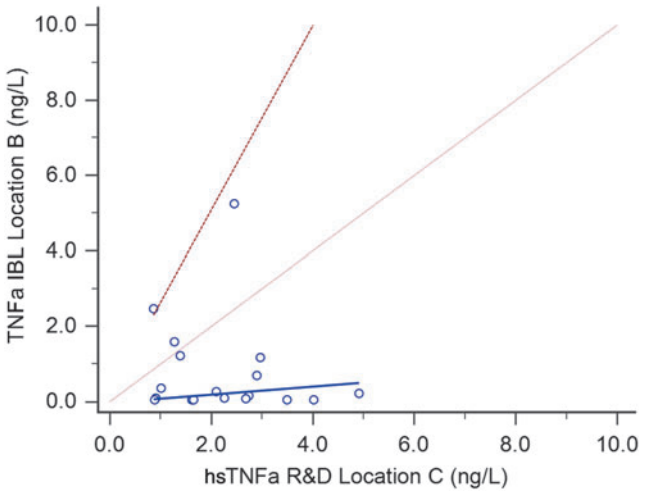

FIG. 7. Passing–Bablok correlation for plasma hsTNFa measured with R&D ELISA (location C) and IBL ELISA (location B). Stored hsTNFa samples measured at two locations using different ELISAs. Location B used the IBL ELISA and location C used the R&D ELISA. Sixteen of the 240 samples were available for analysis; the other samples were below the detection limit of the IBL ELISA.

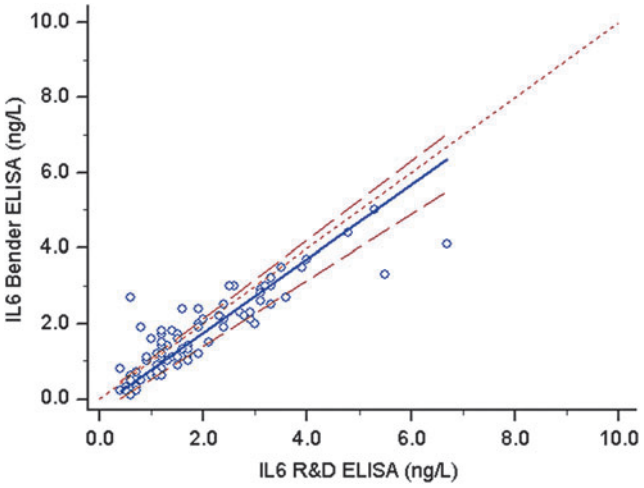

FIG. 8. Confirmation study showing Passing–Bablok correlation for plasma hsIL6 measured with R&D ELISA versus Bender MedSystems ELISA in 80 obese subjects participating in a weight reduction program. Stored hsIL6 samples measured using both the R&D ELISA and the Bender MedSystems ELISA.

Discussion

In the present study, we compared different assays for the measurement of the inflammatory biomarkers, hsCRP, hsIL6, and hsTNFα, and assessed the effect of storage time on the reproducibility of those biomarkers. Our data showed that short- to medium-term storage (less than 2 years, more than 4 years) did not influence the plasma levels of hsCRP and hsIL6 measured by nephelometry and by ELISA, respectively, although small differences between two hsIL6 ELISAs were identified. Concerning the hsTNFα measurements, at one location, the majority of samples was lost due to an analytical error, while the IBL ELISA failed to provide results within the detection limit of the assay.

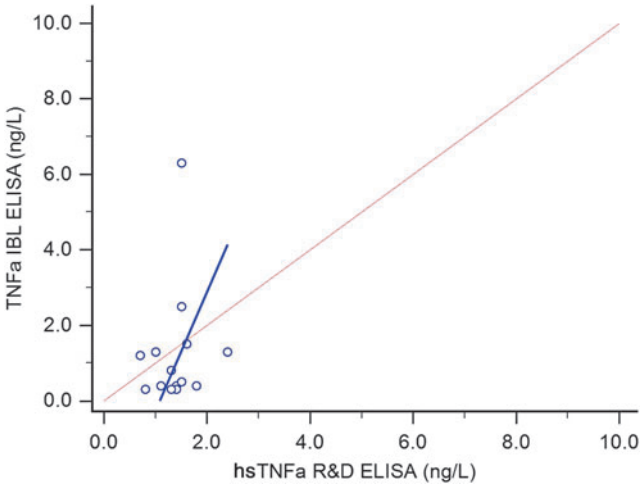

FIG. 9. Confirmation study showing Passing–Bablok correlation for plasma hsTNFα measured with R&D ELISA versus IBL ELISA in 80 obese subjects participating in a weight reduction program. Stored hsTNFa samples measured using both the R&D ELISA and the IBL ELISA. Fourteen of the 80 samples were available for analysis; the other 66 were below the detection limit of the IBL ELISA.

hsCRP is frequently measured in clinical and epidemiological studies. We observed only a moderate agreement between results of nephelometry and ELISA. Similar findings have been reported in a study by Lopez-Campos et al.[16] who reported higher hsCRP concentrations when measured by nephelometry compared with measurements by ELISA.

Our results with the ELISA method were in agreement with Lopez-Campos et al. clearly showing an upper limit of detection. For hsCRP concentrations above 25 mg/L, a sample needs to be diluted and reanalyzed, which is not the case with nephelometry.

Nevertheless, our results of the stored samples showed excellent sample stability after >4 years of storage at −80°C. These results indicate that the single thaw–freeze step had no influence on hsCRP levels. Other studies regarding long-term storage of hsCRP have reported contradictory results.[14] Doumatey et al. showed that serum hsCRP concentrations remained stable with storage for up to 11 years at −80°C.[14] This was, however, in disagreement with an article from Japan reporting that hsCRP levels increased over time in samples stored at −80°C for 13.8 years.[15]

Measurement of hsIL6 with the same R&D ELISA method in different laboratories showed good agreement. However, the fact that 38 samples gave results below the detection limit in one laboratory should be taken into account. It should be noted that we have no data on hsIL6 levels measured on the day of blood collection. There is remarkably little information on studies investigating different assays or the influence of storage time on measurement of IL6. A recent study by Hardikar et al. showed moderate stability of IL6 samples that were stored at −80°C for less than 13 years.[19]

A previous study examining the influence of short-term storage of several biomarkers showed excellent stability for TNFα in samples stored at −80°C for 90 days.[20] Although this is encouraging, the relevance of these data for biobanking, where samples have been or will be stored for many years, is limited. As was the case for hsIL6, between-laboratory variation of the R&D hsTNFa ELISA was very small. When biomarker measurements are performed on stored biobank samples, the amount of sample needed for a specific measurement is of great importance. This was the main reason why we chose the Bender MedSystems hsIL6 assay for our comparison studies as the assay required only 50 μL of sample. In contrast, the R&D ELISAs required 100 and 200 μL for hsIL6 and hsTNFa, respectively. A head-to-head comparison between the Bender MedSystems and R&D ELISAs demonstrated a reasonable agreement, although the Bender MedSystems assay gave significantly lower plasma levels of hsIL6.

The majority of hsTNFα samples at location A were lost due to an error by a technician, whereas at location B, many samples were below the detection limit of the assay despite meticulously following specific instructions. Our replication study confirmed that this was not an incidental finding. Despite the low amount of sample needed, we can, currently, not recommend the use of this specific assay. When choosing an assay, it is advisable to thoroughly test all assays needed for the study before measuring samples obtained from long-term storage in biobanks. In addition, the traceability of the standardization of the assay is also very important. These samples are usually expensive samples, with limited amounts of sample material available in storage. For testing purposes, we therefore recommend the use of sample material obtained in

daily practice, samples obtained from (paid) volunteers, or anonymized leftover material from a laboratory or blood bank facility. As far as we know, the LifeLines facility has not split any samples for the purpose of repeated prospective follow-up measurements within the same individual.

In summary, plasma hsCRP and hsIL6 samples showed good stability when stored for either less than 2 years or more than 4 years at −80°C. Even when the same ELISA method was used, there were small variations in results reported by different laboratories. Although it appears attractive to utilize assays that need only small volumes of samples, such assays should be rigorously tested before large sample sets are measured.

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Part of this article has been published on the BioShaRE website:

www.bioshare.eu/sites/default/files/1/D5.9%20Scientific%20paper%20on%20the%20use%20and%20utility%20of%20inflammatory%20markers%20in%20Healthy%20Obese%20individuals.pdf

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Author Disclosure Statement

No competing financial interests exist.

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